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## ADRENERGIC AND ADRENOCORTICAL RESPONSES TO FLUOTHANE AND CYCLOPROPANE\*

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Classic teaching has for years supported the opinion that catechol amines are increased during, and presumably as a result of, general anesthesia. Much of the support for this opinion has come from intelligent application of inference, from bioassay studies and measurements of depletion of adrenal glands, again presumably in response to general anesthesia. Sympathomimetic responses during general anesthesia are quite familiar, as manifested by tachycardia, elevation of blood pressure, increased sudomotor activity, and even increased pilomotor activity. There is a growing controversy as to the beneficial or deleterious effects to be obtained from this sympathomimetic, or adrenergic, response to general anesthesia.

Clinically, this adrenergic response appears diminished or absent during Fluothane anesthesia. This clinical impression prompted a study of adrenergic responses to Fluothane anesthesia in dogs.

Classically, it is taught that cyclopropane anesthesia evokes a strong adrenergic response; therefore, this response to cyclopropane anesthesia in dogs was chosen as a companion study for comparison.

### METHODS

Two groups of 20 mongrel dogs without premedication were anesthetized for the study. Each group was anesthetized with a partial

rebreathing system incorporating a circle absorber. In each group, the anesthetic compound to be studied was added to a mixture of nitrous oxide flowing at 2 L. per minute and oxygen flowing at 2 L. per minute. Every attempt was made during the period of anesthesia to maintain adequate ventilation with spontaneous respiration.

The dogs in the group receiving Fluothane anesthesia had anesthesia induced with open drop Fluothane, their tracheae intubated, and Fluothane added from an F.N.S. vaporizer to the previously mentioned nitrous oxide-oxygen mixture to deliver a 2 per cent Fluothane concentration; anesthesia was maintained with this concentration.

The dogs in the group receiving cyclopropane anesthesia were intubated while awake, and occasionally 5 to 10 mg. of succinyl choline chloride were used intravenously to facilitate tracheal intubation. When respiration seemed decreased as a result of the succinyl choline, artificial ventilation with oxygen was maintained until normal spontaneous respiratory movements were established. After endotracheal intubation, anesthesia was induced by adding cyclopropane to the nitrous oxide-oxygen mixture to provide a 25 per cent cyclopropane concentration. After third level anesthesia was reached, anesthesia was maintained with 15 to 25 per cent cyclopropane.

During the period of anesthesia, a study in wound healing was begun by the Department of Surgery. Thoracotomy incisions were made in 20 of the dogs anesthetized, by cautery alone for

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the incisions in 10 dogs and by standard scalpel incisions in another 10 dogs. The thoracotomy incisions were closed surgically. The remaining 20 dogs had standard scalpel laparotomy incisions made and closed surgically. In all dogs, inguinal incisions were made and a femoral artery cannulated, either under local anesthesia before induction of general anesthesia or during the period of general anesthesia.

The femoral artery was used as a site for collecting four arterial blood samples during the study, either by direct arterial puncture or from the artery cannula referred to above. The control sample was drawn immediately before general anesthesia was induced. The second sample was obtained as soon as surgical anesthesia levels were reached and the femoral artery cannulated, the two points usually being arrived at simultaneously. The third sample was drawn after surgical anesthesia had been maintained for 1 hour, the thoracotomy or laparotomy incision having been completed in this time. Immediately after the third sample was obtained, the dogs were allowed to awaken, as manifested by barking and limb movements. The last sample was obtained 4 hours after emergence from anesthesia.

The four samples were used for the following measurements: pH, as measured with a Beckman pH meter; oxygen and carbon dioxide content as measured by the method of Van Slyke; catechol amines, as measured by the method of Weil-Malherbe and Bone<sup>3,4</sup>; and 17-hydroxycorticosteroids (17-OHCS), both free and conjugated, as measured by the methods of Nelson and Samuels<sup>2</sup> and Bongiovanni.<sup>1</sup>

Arterial samples were used rather than venous samples for studies of catechol amines and 17-OHCS because of the possibility of multiple sites of production of these compounds. Arterial blood then should represent a fair pooling of the products of these multiple sites.

Sampling from various component venous beds may have given greater specificity to the sampling, but this study was more concerned with total body elaboration of catechol amines and 17-OHCS.

The method of measurement of catechol amines is subject to error, in that other catechol derivatives (dihydroxyphenylethylamine, dihydroxyphenyl acetic acid) may interfere if they are present in the plasma. The figures reported for catechol amines must be accepted as maximal

values, possibly representing traces of these other catechol derivatives. Another source of error may be incurred if the ratio of epinephrine to norepinephrine (or *vice versa*) exceeds 20:1. In greater ratios, the determination of the lesser hormone has a reduced reliability.

At the conclusion of this study, it was discovered that, through an error in identification, three dogs in the group anesthetized with Fluothane were given cortisone in preparation for an unrelated study. These dogs were omitted from this report.

#### RESULTS

**Blood gases and pH.** The results of sampling arterial pH, carbon dioxide content and oxygen content showed variations from sample to sample in each dog. These individual variations were calculated, and average deviations rather than absolute values are presented as representative of the groups.

The pH remained remarkably constant in all dogs, the extremes of single determinations ranging from 7.46 to 7.35. In no single dog did the pH vary by more than 0.04 pH unit, the average variation being 0.014 pH unit. There was no consistent direction of variation.

In dogs under Fluothane anesthesia, carbon dioxide content variations within each dog ranged from 0.11 volume per cent to 12.98 volume per cent, with an average variation of 5.79 volume per cent.

The group of dogs under cyclopropane anesthesia showed a wider range of variation in carbon dioxide content. The average variation of carbon dioxide content was 14.24 volume per cent, but the degree of change varied from 2.64 volume per cent to 37.62 volume per cent. There was no consistent trend in these variations.

Arterial oxygen content in dogs anesthetized with Fluothane varied as much as 9.30 volume per cent and as little as 0.46 volume per cent. The average variation was 5.03 volume per cent. Dogs anesthetized with cyclopropane showed very similar variations in oxygen content, varying as much as 10.50 volume per cent and as little as 1.08 volume per cent. The average variation of oxygen content in this group was 4.32 volume per cent. Again, no consistent trend in deviations could be demonstrated. Results of measurements of pH, oxygen content and carbon dioxide content are presented in tables 1 and 2.

**Catechol amines.** Measurements of catechol

TABLE 1

*Arterial pH, oxygen content and carbon dioxide content in dogs anesthetized with cyclopropane*

Dog No.	pH				Oxygen Content				Carbon Dioxide Content			
	C*	1*	2*	3*	C	1	2	3	C	1	2	3
1	7.41	7.40	7.39	7.40	15.22	17.16	16.97	17.18	37.89	34.18	34.33	38.18
2	7.40	7.39	7.40	7.40	17.30	21.83	22.30	21.23	42.22	40.07	42.47	36.76
3	7.39	7.40	7.41	7.41	17.79	18.11	19.53	18.79	37.41	38.27	39.40	38.90
4	7.39	7.36	7.35	7.36	15.45	16.60	15.93	14.38	22.18	29.26	38.16	32.42
5	7.41	7.41	7.40	7.40	11.65	16.19	16.60	10.64	36.05	35.00	33.42	34.80
6	7.39	7.40	7.38	7.39	14.99	17.03	15.56	12.67	17.73	17.96	32.28	26.59
7	7.40	7.40	7.39	7.39	15.27	17.03	16.29	17.11	34.92	47.47	66.82	48.52
8	7.44	7.45	7.44	7.46	15.66	17.66	17.27	17.43	28.97	33.03	38.52	35.01
9	7.42	7.41	7.41	7.40	10.78	13.16	13.40	10.92	40.86	33.75	34.06	38.04
10	7.40	7.40	7.39	7.40	13.90	14.98	13.47	14.27	35.72	21.01	25.51	28.33
11	7.41	7.40	7.40	7.40	18.05	18.15	15.37	16.35	44.84	34.32	39.04	71.94
12	7.42	7.41	7.41	7.39	6.82	8.24	8.34	5.83	41.65	19.66	22.08	36.70
13	7.39	7.39	7.38	7.40	10.01	15.91	10.61	9.24	35.83	20.47	29.08	22.90
14	7.41	7.41	7.40	7.41	22.16	29.21	23.73	22.87	32.12	23.98	23.67	37.34
15	7.40	7.40	7.39	7.40	13.15	15.90	15.76	11.78	40.46	37.21	37.16	34.99
16	7.41	7.39	7.39	7.40	17.08	19.74	17.79	17.97	33.49	26.58	32.26	31.31
17	7.41	7.40	7.39	7.40	16.57	18.97	17.86	14.31	43.66	39.93	37.90	17.86
18	7.42	7.41	7.41	7.41	19.46	24.96	18.80	18.98	41.40	31.59	37.26	38.94
19	7.41	7.41	7.41	7.40	15.01	17.84	17.21	16.33	32.97	36.38	34.47	35.81
20	7.40	7.40	7.39	7.40	30.39	14.40	13.61	9.89	33.52	12.29	37.69	35.87

\* Blood samples: control and samples 1, 2 and 3.

TABLE 2

*Arterial pH, oxygen content and carbon dioxide content in dogs anesthetized with Fluothane*

Dog No.	pH				Oxygen Content				Carbon Dioxide Content			
	C	1	2	3	C	1	2	3	C	1	2	3
1	7.41	7.40	7.39	7.40	18.66	23.14	24.67	24.00	45.97	45.34	43.28	44.87
2	7.40	7.39	7.40	7.40	15.96	17.24	16.79	11.94	53.82	56.73	57.85	58.65
3	7.39	7.40	7.41	7.41	14.42	17.40	17.73	13.64	51.32	47.61	50.26	48.47
4	7.39	7.36	7.35	7.36	18.85	19.19	19.31	19.83	42.99	44.14	42.65	42.87
5	7.41	7.41	7.40	7.40	19.58	18.61	17.43	12.40	49.99	49.02	43.53	56.11
6	7.39	7.40	7.38	7.39	8.78	8.78	10.98	8.99	37.99	34.18	34.33	38.18
7	7.40	7.40	7.39	7.39	8.60	10.33	10.69	7.61	37.60	39.90	29.88	32.18
8*	7.44	7.45	7.44	7.46	1.66	3.74	3.81	0.48	43.89	40.78	45.87	40.47
9*	7.42	7.41	7.41	7.40	12.18	14.41	14.50	9.91	37.42	39.40	38.27	38.90
10*	7.40	7.40	7.39	7.40	13.21	18.11	16.79	18.00	60.78	60.66	60.89	60.78
11	7.41	7.40	7.40	7.40	17.40	18.36	19.53	18.63	41.16	43.85	43.44	41.41
12	7.42	7.41	7.41	7.39	15.59	18.09	16.26	12.41	41.94	42.10	33.72	48.77
13	7.39	7.39	7.38	7.40	13.45	18.46	21.94	18.62	44.22	43.77	42.31	38.36
14	7.42	7.41	7.40	7.41	13.92	17.78	15.80	17.21	39.21	39.35	40.78	39.32
15	7.40	7.40	7.39	7.40	14.60	17.15	20.11	11.81	37.81	29.87	36.44	39.28
16	7.41	7.39	7.39	7.40	16.22	15.36	20.42	18.56	31.90	42.85	44.22	40.82
17	7.41	7.40	7.39	7.40	14.60	15.83	14.41	11.75	36.87	39.30	38.54	40.79
18	7.42	7.41	7.41	7.41	16.42	14.16	17.97	10.18	41.71	34.21	37.01	45.34
19	7.41	7.41	7.41	7.40	15.22	17.71	16.15	17.25	42.24	43.75	42.89	42.40
20	7.40	7.40	7.39	7.40	16.25	21.57	16.78	12.27	43.43	39.95	43.81	37.96

\* Dogs 8, 9 and 10 omitted.

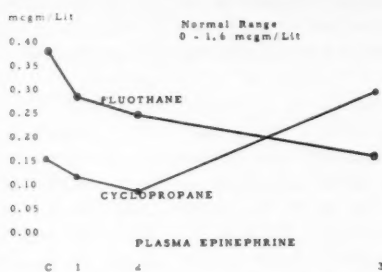


FIG. 1. Average trends of arterial plasma epinephrine in dogs anesthetized with cyclopropane and Fluothane.

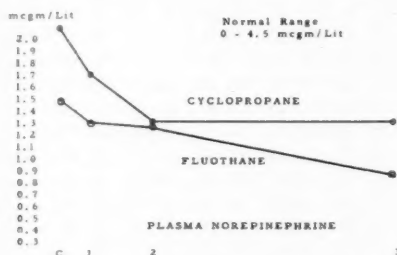


FIG. 2. Average trends of arterial plasma norepinephrine in dogs anesthetized with cyclopropane and Fluothane.

amines produced results that were unexpected. As seen in figure 1, average plasma epinephrine values were reduced from control levels throughout the period of anesthesia, both with cyclopropane and with Fluothane. In the group of dogs anesthetized with Fluothane, the average values decreased from a control value of 0.38  $\mu\text{g. per L.}$  to 0.29  $\mu\text{g.}$  in the postinduction sample, to 0.25  $\mu\text{g.}$  after 1 hour of anesthesia, and 0.16  $\mu\text{g.}$  in the 4th-hour postanesthesia sample. In the group of dogs anesthetized with cyclopropane, the average values decreased from a control of 0.16  $\mu\text{g.}$  to 0.13  $\mu\text{g.}$  at the postinduction sampling, to 0.09  $\mu\text{g.}$  after 1 hour of anesthesia, and then increased above control values to 0.29  $\mu\text{g.}$  at the 4th hour postanesthesia sampling.

In both groups of dogs there were only two instances during the entire study in which plasma epinephrine exceeded a normal range of 0 to 1.6  $\mu\text{g. per L.}$  One dog in the Fluothane group had a control value of 1.67  $\mu\text{g. per L.}$ , and a dog in the cyclopropane group had a 4th-hour postanesthesia value of 2.71  $\mu\text{g. per L.}$  In no instance did plasma epinephrine values exceed the accepted normal ranges during the period of anesthesia.

Average values for norepinephrine are shown in figure 2. Tables 3 and 4 contain measurements of epinephrine and norepinephrine for all dogs of both groups. Beginning with an average control plasma norepinephrine value in the Fluothane group of 1.50  $\mu\text{g.}$ , there was a decrease to 1.34  $\mu\text{g.}$  in the postinduction sample, then to 0.89  $\mu\text{g.}$  in the 4th-hour postanesthesia sample. The average control value for the cyclopropane group was 5.08  $\mu\text{g.}$  This value decreased to 1.70  $\mu\text{g.}$  after induction of anesthesia, then to 1.34  $\mu\text{g.}$  after 1 hour of anesthesia, and to 1.32  $\mu\text{g.}$  in the 4th-hour postanesthesia sample.

There were three instances in which norepinephrine exceeded the accepted normal range of 0 to 5.6  $\mu\text{g. per L.}$  on the first sample after anesthesia was begun. His control value was 2.39  $\mu\text{g. per L.}$  One dog in the Fluothane group had a control value of 4.75  $\mu\text{g. per L.}$  Another dog of the Fluothane group was found to have a level of 4.79  $\mu\text{g. per L.}$  after 1 hour of anesthesia. His control measurement of norepinephrine was 1.6  $\mu\text{g. per L.}$

TABLE 3

*Plasma epinephrine and norepinephrine contents in dogs anesthetized with cyclopropane*

Dog No.	Epinephrine				Norepinephrine			
	C	1	2	3	C	1	2	3
	$\mu\text{g./L.}$				$\mu\text{g./L.}$			
1	0.00	0.00	0.00	0.00	2.39	4.75	2.55	2.55
2	0.00	0.00	0.00	0.00	0.00	0.83	0.00	0.00
3	0.00	0.00	0.00	1.15	3.33	1.36	0.00	0.00
4	0.00	0.00	0.00	0.00	3.00	0.00	0.00	2.57
5	0.00	0.00	0.00	2.71	4.14	3.04	3.60	1.08
6	0.02	0.03	0.00	0.00	1.76	1.63	1.60	2.00
7	0.26	0.20	0.14	0.00	2.17	1.81	2.72	2.94
8	0.00	0.00	0.00	0.00	3.01	3.42	2.97	3.00
9	0.08	0.10	0.08	0.00	1.11	1.00	1.23	1.02
10	0.00	0.00	0.00	0.00	0.61	0.00	0.00	0.00
11	1.23	1.20	1.20	0.98	1.66	1.68	1.45	1.70
12	0.04	0.00	0.00	0.00	0.00	0.03	0.00	0.00
13	0.00	0.00	0.00	0.00	3.06	1.15	2.42	2.30
14	0.09	0.00	0.00	0.00	2.08	2.00	2.00	1.80
15	1.10	0.90	0.39	0.98	2.87	2.90	2.00	2.60
16	0.12	0.10	0.00	0.00	1.61	1.20	0.90	0.00
17	0.00	0.00	0.00	0.00	2.49	0.51	0.00	1.79
18	0.02	0.00	0.00	0.00	0.06	0.18	1.46	0.00
19	0.00	0.00	0.00	0.00	1.71	1.00	0.00	0.00
20	0.00	0.00	0.00	0.00	4.02	4.02	1.85	0.00



TABLE 4

Plasma epinephrine and norepinephrine contents in dogs anesthetized with Fluothane

Dog No.	Epinephrine				Norepinephrine			
	C	1	2	3	C	1	2	3
	$\mu\text{g./L.}$				$\mu\text{g./L.}$			
1	0.46	0.52	0.07	0.00	0.00	0.00	0.00	0.00
2	1.67	1.00	1.10	0.76	0.00	0.00	0.00	0.00
3	0.00	0.00	0.09	0.00	1.60	1.72	4.79	2.17
4	0.07	0.00	0.00	0.60	0.00	0.64	0.64	0.00
5	0.58	0.55	0.00	0.00	0.05	0.00	0.00	0.00
6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
7	0.00	0.00	0.18	0.00	0.00	0.00	0.19	0.00
8*	0.00	0.00	0.00	0.02	3.51	3.48	2.58	0.64
9*	0.00	0.00	0.00	0.00	1.12	1.12	0.70	1.28
10*	0.14	0.10	0.00	0.00	2.81	2.09	2.00	0.00
11	0.51	0.40	0.51	0.38	3.00	2.40	2.00	2.61
12	0.50	0.00	0.00	0.00	2.10	1.31	1.04	0.91
13	1.28	1.01	0.90	0.00	1.20	2.61	1.50	1.01
14	0.00	0.00	0.13	0.00	2.74	1.92	1.81	0.70
15	0.00	0.00	0.00	0.00	1.61	0.00	0.00	0.00
16	0.00	0.00	0.00	0.00	0.90	0.87	0.64	1.03
17	0.91	0.84	0.51	0.00	4.16	3.61	3.00	3.53
18	0.04	0.00	0.00	0.00	0.64	0.00	0.00	0.00
19	1.48	1.40	1.50	1.41	4.70	4.21	3.71	3.96
20	0.00	0.00	0.00	0.00	0.00	0.81	0.20	0.00

\* Dogs 8, 9 and 10 omitted.

**Plasma corticoids.** The measurements of free and conjugated 17-OHCS provided unexpected results also. The accepted normal range for free 17-OHCS by this method is 5 to 15  $\mu\text{g.}$  per 100 ml. In control samples, this range was exceeded by five dogs in the cyclopropane group and one dog in the Fluothane group. Control levels below normal were found in two dogs of the cyclopropane group and one dog in the Fluothane group.

In figure 3 are shown the average values for free 17-OHCS. The values for the four samples in the Fluothane group are 7.04  $\mu\text{g.}$  per 100 ml., 8.57  $\mu\text{g.}$ , 7.97  $\mu\text{g.}$ , and 6.37  $\mu\text{g.}$  The values for the four samples in the cyclopropane group are 12.57  $\mu\text{g.}$  per 100 ml., 23.22  $\mu\text{g.}$ , and 17.79  $\mu\text{g.}$

Dogs under cyclopropane anesthesia generally showed an initial rise of 17-OHCS on induction of anesthesia. Only two dogs in the cyclopropane group failed to show an increase to above normal values in this postinduction sampling. The rise on induction of Fluothane anesthesia was less pronounced than that seen with cyclopropane. Only three dogs in the Fluothane group exceeded

the normal range in postinduction sampling. After 1 hour of anesthesia, the average free 17-OHCS values in both groups had fallen to near control levels. Four dogs in the Fluothane group and eight in the cyclopropane group exceeded the normal range on this sample.

Samples at the 4th postanesthesia hour showed widely divergent results. Dogs in the Fluothane group invariably continued the downward trend of free 17-OHCS, whereas dogs of the cyclopropane group generally showed an increase to values above normal. Only four dogs in the cyclopropane group failed to exceed normal values for this last sampling. None of the dogs in the Fluothane group exceeded the normal range in this last sampling.

Measurements of conjugated 17-OHCS showed the same general trends as the values for free 17-OHCS. In figure 4 are shown the average values of conjugated 17-OHCS. In the Fluothane group, the average values for the four samples are 2.67  $\mu\text{g.}$  per 100 ml., 3.33  $\mu\text{g.}$ , 3.38  $\mu\text{g.}$ , and 3.02

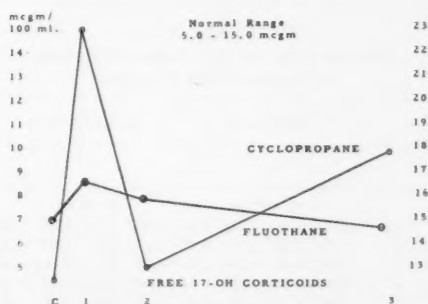


FIG. 3. Average trends of arterial free 17-OHCS in dogs anesthetized with cyclopropane and Fluothane. The scale to the left of the figure represents Fluothane; the scale on the right, cyclopropane.

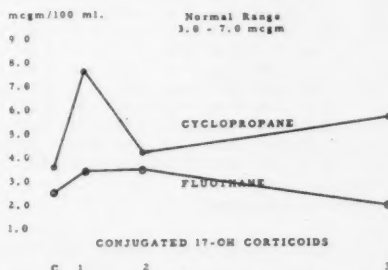


FIG. 4. Average trends of arterial conjugated 17-OHCS in dogs anesthetized with cyclopropane and Fluothane.

TABLE 5  
Plasma 17-hydroxycorticosteroids in dogs  
anesthetized with cyclopropane

Dog No.	Free Steroid				Conjugated Steroid			
	C	1	2	3	C	1	2	3
	$\mu\text{g./100 ml.}$				$\mu\text{g./100 ml.}$			
1	14.50	20.50	18.75	17.25	2.50	7.50	7.50	7.25
2	7.25	19.98	19.47	9.65	0.00	7.23	4.99	0.00
3	18.00	28.14	16.40	19.80	5.80	9.00	7.00	6.00
4	3.00	15.00	00.00	9.80	0.00	7.00	0.00	0.00
5	9.95	35.50	23.00	20.50	3.75	12.50	10.00	8.75
6	14.40	30.20	3.75	8.70	5.80	10.00	0.00	0.00
7	9.80	23.00	11.00	16.40	3.00	8.40	4.40	7.00
8	12.40	19.80	17.80	16.00	5.80	6.00	5.80	7.00
9	11.80	23.00	6.00	17.80	4.40	8.40	2.50	5.90
10	7.00	8.40	5.80	17.76	2.50	3.00	0.00	5.42
11	16.00	20.80	15.00	16.80	6.00	7.00	6.00	6.00
12	12.40	21.00	9.99	16.80	4.40	7.80	0.00	9.66
13	4.40	9.00	3.00	3.00	0.00	3.00	0.00	0.00
14	22.40	43.00	30.50	38.75	8.00	10.50	12.50	11.25
15	10.00	36.00	00.00	22.00	3.00	11.80	0.00	7.80
16	18.00	20.40	6.00	18.40	7.25	7.00	0.00	7.00
17	22.97	26.30	26.64	30.63	4.99	7.32	7.32	9.65
18	14.40	30.40	17.80	23.00	3.00	9.80	4.40	6.00
19	11.80	16.00	12.90	18.00	3.00	4.40	4.07	5.66
20	11.00	18.00	15.00	15.00	2.00	5.80	3.00	3.00

TABLE 6  
Plasma 17-hydroxycorticosteroids in dogs  
anesthetized with Fluothane

Dog No.	Free Steroid				Conjugated Steroid			
	C	1	2	3	C	1	2	3
	$\mu\text{g./100 ml.}$				$\mu\text{g./100 ml.}$			
1	20.60	18.30	3.70	9.60	5.50	3.30	0.00	3.30
2	8.70	2.50	5.80	5.00	2.50	0.00	0.00	0.00
3	3.70	5.50	0.00	2.50	0.00	2.50	0.00	0.00
4	3.30	0.00	0.00	0.00	4.90	13.70	14.90	12.20
5	7.50	2.50	5.50	2.50	7.50	0.00	0.00	0.00
6	9.60	14.70	19.70	11.20	0.00	4.50	10.50	3.00
7	9.60	11.00	9.00	10.00	3.75	3.00	3.00	3.33
8*	38.00	35.00	36.50	42.20	8.00	7.43	7.20	7.20
9*	22.40	21.50	38.40	44.80	9.10	8.00	10.00	10.50
10*	64.00	56.00	73.00		2.00	8.69	8.00	
11	7.25	3.70	5.50	10.00	3.75	0.00	2.50	3.75
12	3.75	2.50	2.50	00.00	2.50	0.00	0.00	0.00
13	00.00	14.50	8.75	2.50	0.00	5.00	0.00	0.00
14	5.50	9.75	7.97	2.00	2.50	3.75	3.38	0.00
15	3.00	2.50	2.50	00.00	0.00	0.00	0.00	0.00
16	12.25	15.50	15.50	13.98	3.75	5.60	3.75	3.33
17	11.25	15.50	20.00	3.60	2.50	5.50	7.50	0.00
18	6.25	9.80	10.50	00.00	3.75	4.40	4.40	0.00
19	7.50	13.75	16.50	2.50	2.50	5.50	7.25	0.00
20	00.00	3.75	10.00	15.00	0.00	0.00	3.75	5.50

\* Dogs 8, 9 and 10 omitted.

$\mu\text{g.}$  In the cyclopropane group, the average values for the four samples are 3.76  $\mu\text{g.}$  per 100 ml., 7.67  $\mu\text{g.}$ , 4.07  $\mu\text{g.}$  and 5.66  $\mu\text{g.}$

Only four dogs in the cyclopropane group failed to exceed normal values on at least one sampling.

Only five dogs in the Fluothane group exceeded normal values for any of the four samplings. These data are presented in tables 5 and 6.

#### DISCUSSION

The purpose of measuring pH, arterial oxygen content and arterial carbon dioxide content was to reflect the adequacy of pulmonary ventilation, since hypoxia and/or hypercarbia could significantly influence levels of catechol amines and 17-OHCS. We feel that at least adequate pulmonary ventilation was achieved throughout the study.

The results of this study failed to demonstrate, by chemical detection, an increase in catechol amines of significant proportion in response to Fluothane or cyclopropane anesthesia. The appearance of catechol amines in the circulation certainly can be evanescent. Presumably, an increase in catechol amines could escape detection by the means used in this study. It has been proposed that the clinical responses seen which suggest increased adrenergic activity (tachycardia, increased vasomotor activity during general anesthesia) may be due to (1) increased catechol amine production, (2) delayed excretion or destruction of catechol amines, (3) elaboration of a system involving compounds other than epinephrine and norepinephrine, or (4) increased sensitivity of the substrate on which catechol amines might have their effect.

A second interesting group of findings resulting from this study were the alterations of 17-OHCS values during and after anesthesia. The increases shown in this study are as one might anticipate. The fact that changes in 17-OHCS and catechol amines are not parallel is an accepted fact. This study indicates that the anticipated increase in 17-OHCS levels in plasma definitely was suppressed for at least 4 hours after Fluothane anesthesia. The ratio of free to conjugated 17-OHCS was roughly the same throughout the study, suggesting that formation or liberation, rather than destruction, was influenced during the postanesthesia period.

#### SUMMARY

Studies of adrenal activity as reflected by the measurement of plasma catechol amines and 17-hydroxycorticosteroids (17-OHCS) levels are reported for 17 dogs anesthetized with Fluothane and 20 dogs anesthetized with cyclopropane.

Catechol amine levels were not elevated during the period of anesthesia with either cyclopropane or Fluothane; on the contrary, these levels decreased steadily for as long as anesthesia was maintained. This decrease in catechol amine levels persisted for at least 4 hours after fluothane anesthesia.

The plasma 17-OHCS levels were decreased for at least 4 hours after Fluothane anesthesia, but were elevated after cyclopropane anesthesia.

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## STRANGULATION OBSTRUCTION: EXPERIMENTAL FINDINGS WITH CLINICAL IMPLICATIONS\*

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The high mortality rate which attends those patients whose intestinal circulation is obstructed has been a source of concern to surgeons for many decades. When frank gangrene occurs with leakage of bowel content into the peritoneal cavity, the outlook is indeed exceedingly grave. In spite of attempts by clinicians to institute early operation in the care of patients with intestinal obstruction, many of these individuals are offered surgery only late in the course of their illnesses. The following is a consideration of certain experimental findings which relate to the ultimate outcome after gangrenous bowel obstruction.

### FORMATION OF PERITONEAL FLUID

Intestinal circulatory arrest most commonly results from interference with the venous drainage of a segment of bowel. Primary mesenteric venous thrombosis may occur, but most commonly external pressure upon the veins is responsible. The latter mechanism may occur when bowel is trapped by adhesions or by the neck of a hernia. Because of the relatively low pressure within the lumen, venous occlusion occurs first, with arterial arrest coming on later. Shortly after the occurrence of intestinal venous obstruction, the peritoneal fluid is yellow and bears considerable resemblance to blood plasma. After a period of several hours, the fluid becomes pink, and late in the course of strangulation it assumes a dark red color. Mesenteric arterial occlusion produces considerably smaller quantities of peritoneal fluid than the variety described above (fig. 1).

### TOXICITY OF PERITONEAL FLUID

It was found that after closed loop strangulation of the ileum in dogs, most of the animals died within 24 to 30 hours. The peritoneal cavities of these animals yielded from 1 to 300 ml. of dark, foul fluid.<sup>9, 10</sup> When similar strangulated segments of ileum were placed inside a plastic

bag before they were returned to the abdominal cavity so that peritoneal exposure could not occur, the life of the animal was considerably prolonged.<sup>4</sup> Injection of the fluid recovered from the plastic bag into the peritoneal cavities of normal dogs revealed this material to be highly toxic in amounts as small as 3 ml. per kg. (fig. 2).

Peritoneal fluid was recovered after strangulation of the stomach, duodenum, jejunum, ileum and colon in separate animals. The toxicity of the resulting fluid was found to increase from the upper to the lower levels of the gastrointestinal tract.<sup>20</sup>

### LETHAL COMPONENT OF STRANGULATION FLUID

The question of the lethal component of strangulation fluid has prompted much investigative work as well as many reports in the surgical literature. The role of altered hemoglobin pigments in the lethal action of strangulation fluid has been the subject of much interest. The following findings cast doubt upon the thesis that blood elements play a responsible role in the toxic manifestation of strangulation obstruction. Twenty normal dogs were divided into two equal groups. A 10-cm. segment of ileum was dropped into the peritoneal cavity of each animal. The first group of animals received an ileal segment from which all blood elements had been removed by perfusion of the artery with isotonic saline. The second group was exposed to a segment of ileum which was thoroughly filled with blood by ligation of the vein 15 minutes before division of the artery. The mean survival time for the two groups of animals was essentially the same.<sup>2</sup>

*Exotoxins.* Bacterial exotoxins have received considerable attention from various investigators with regard to their part in the fatal outcome of strangulation obstruction. Tanturi and associates<sup>22</sup> reported the identification of the  $\alpha$ -toxin of *Clostridium welchii* in peritoneal fluid resulting from late strangulation obstruction. Cohn<sup>18</sup> was successful in obtaining a lethal outcome by the placement of sterile divitalized bowel along with

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## COMMON CAUSES OF BOWEL GANGRENE

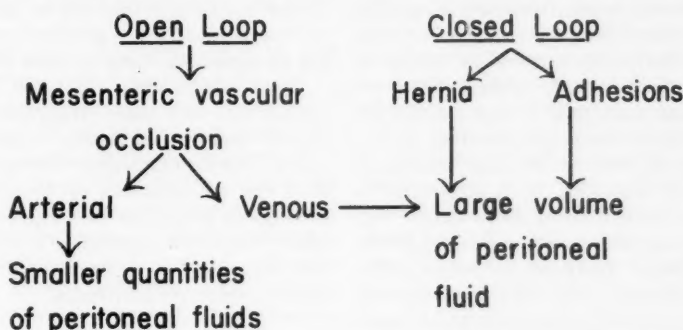


FIG. 1. Lesions most frequently associated with bowel gangrene.

*C. welchii* organisms into the peritoneal cavity of normal dogs. Our experience has caused us to maintain considerable reservation concerning the assignment of a major role to exotoxins in the pathophysiology of strangulation obstruction. Physiologic changes *in vivo* which result from the injection of exotoxins differ considerably from those observed after exposure to strangulation fluid.<sup>13</sup> When strangulation fluid was passed through a Seitz filter, the lethal properties were eliminated. One would not expect this process to remove exotoxins. In fact, when exotoxins from *C. welchii* were added to unaltered strangulation fluid, a toxic filtrate was obtained after passage through the Seitz filter. Furthermore, the injection of polyvalent *C. welchii* antitoxin together with strangulation fluid was not effective in prolonging the life of experimental animals. A consideration of all these factors indicates that there is insufficient evidence to warrant the use of *C. welchii* antitoxin in the management of clinical strangulation obstruction.

**Bacteria.** Centrifugation of strangulation fluid at 700 rpm for 10 minutes failed to render the supernatant fluid nontoxic.<sup>17</sup> However, when the speed of centrifugation was increased to 17,000 rpm for a similar period, the centrifugate was found to be toxic, and the supernatant material was tolerated well by experimental animals. Microscopic examination of the toxic centrifugate revealed multiple bacterial cells of many varieties. The introduction of antibiotics into the ileal lumen at the time of strangulation resulted in nontoxic peritoneal fluid.<sup>5, 7</sup> Antibiotics are the only agents which have been effective in protect-



FIG. 2. Chances for survival are improved by prevention of exposure to toxic fluid.

ing normal animals against an otherwise lethal dose of strangulation fluid. After peritoneal exposure of normal animals to strangulation fluid, bacteria may be cultured from the blood stream in increasing numbers for 4 to 5 hours.<sup>4</sup> Strangulation fluid obtained from an untreated segment of ileum was found to be effective in immunizing (or increasing the tolerance to the fluid) normal



animals against the usual lethal dose of fluid. This was not true when the fluid used for immunization was obtained after strangulation of a segment of ileum which had been previously treated with antibiotics.<sup>1</sup> The finding of increasing toxicity of strangulation fluid from the upper to the lower gastrointestinal tract further supports the important role of bacteria in this condition.

**Endotoxins.** Because of the large number of Gram negative organisms which are present in strangulation fluid, it is logical to assume that these agents may play a part in the pathophysiology of intestinal strangulation. Certain pathophysiologic changes which have been observed after exposure to fluid are characteristic of endotoxins. A number of therapeutic agents which have been shown to be effective in protecting against deleterious effects of endotoxins show promise of being of value in the treatment of late experimental strangulation obstruction when they are used in conjunction with other measures. Hemagglutination inhibition studies are now being used in an attempt to determine whether or not endotoxins appear in the blood stream of animals with late strangulation obstruction.

#### PHYSIOLOGIC CHANGES IN VIVO

Hill and Stoner<sup>21</sup> observed the depressing effects of obstructed loop content upon the circulating white blood cells. Our studies revealed a similar change after exposure of normal animals to the peritoneal fluid which accumulated as a result of closed loop strangulation of the ileum. A severe, persistent leukopenia was uniformly observed when normal animals received a lethal dose of fluid.<sup>14</sup> Although it was not consistently true, most animals were found to have a relative increase in lymphocytes, as revealed by the differential white cell count. When a sublethal amount of fluid was injected, a moderate leukopenia was observed for about 2 hours, after which a progressive leukocytosis supervened. Leukopenia was also seen immediately after injection of the usual lethal dose of fluid together with antibiotics. However, leukocytosis was observed after about 4 hours, with recovery of the animals. Apparently the antibiotics protected these animals from the toxic agents until a satisfactory leukocytic response could be mobilized. A progressive increase in the concentration of plasma hemoglobin was also noted. No significant alteration of the prothrombin time, blood platelet or clotting time was

noted. The plasma sodium and potassium levels remained unchanged during the period of observation. All animals exhibited an increase in the rate of respiration, a slight rise in temperature, but no significant change in pulse rate.<sup>12</sup>

When contact was established between the peritoneum and toxic strangulation fluid, a marked degree of peritonitis resulted. This was followed by the outpouring of large quantities of fluid into the peritoneal cavity, possibly in an attempt to dilute this irritating material. As a result, there was a progressive decrease in the plasma volume and thiocyanate space and a marked rise in the hematocrit.

#### ANTIBIOTICS

**Neomycin.** This antibiotic was found to be extremely effective in suppressing the toxic properties of peritoneal fluid when it was introduced into the lumen of a segment of ileum at the time of strangulation. Nontoxic fluid also resulted when the neomycin tablets were placed in a plastic bag together with strangulated bowel. Another group of animals received an intraperitoneal injection of neomycin together with the usual lethal dose of strangulation fluid. Sixty per cent of these animals survived, whereas none of the control animals recovered.<sup>7</sup>

**Chloromycetin.** When placed inside the lumen of a segment of strangulated ileum, Chloromycetin was found to be capable of eliminating the toxic properties of the resulting peritoneal fluid. It was also effective in protecting normal animals against an otherwise lethal dose of strangulation fluid.<sup>5</sup>

**Route of administration.** A series of experiments was conducted to evaluate the efficacy of various routes of antibiotic administration after peritoneal exposure to toxic strangulation fluid. All animals received the same amount of fluid and antibiotics. The only variable was the route by which the antibiotic was administered. When penicillin and streptomycin were given intramuscularly, a survival rate of 30 per cent was obtained, whereas 80 per cent of the animals recovered when these antibiotics were injected into the peritoneal cavity. The intramuscular injection of chloramphenicol produced a survival rate of 20 per cent, whereas 40 per cent of the animals recovered when this antibiotic was administered intravenously. After intraperitoneal injection the survival rate was found to be 70 per cent. The use

of kanamycin resulted in survival of 30 per cent of the animals when given intramuscularly, 40 per cent when injected intravenously, and 80 per cent when administered intraperitoneally. Thus, all antibiotics used in these studies gave the best results after intraperitoneal administration.<sup>19</sup>

**Massive antibiotic administration.** Neomycin in the amount of 100 mg. per kg. gave satisfactory protection against strangulation fluid when the dose was 3 ml. per kg. When the dose of fluid was increased to 6 ml. per kg., poor protection was afforded. Increased doses of neomycin were not effective because of the toxicity of this antibiotic. When penicillin was used, satisfactory survival rates were obtained in the presence of progressively increased doses of strangulation fluid, if the amount of antibiotic was also increased. Penicillin (300,000 units per kg.) afforded poor protection when the dose of strangulation fluid reached 12 ml. per kg., but the combined injection of penicillin and neomycin (100 mg. per kg.) gave good results under these circumstances. The combination of penicillin and kanamycin was also found to be more effective than either of the antibiotics alone. These findings thus indicate that massive doses of antibiotics may be effective in protecting against given amounts of strangulation fluid when smaller amounts prove unsatisfactory.<sup>11</sup>

**Delayed antibiotic administration.** The administration of penicillin (100,000 units per kg.) together with 2 ml. per kg. of strangulation fluid resulted in a survival rate of 50 per cent. When the same amount of antibiotic was given 30 minutes after injection of the fluid, the survival rate dropped to 15 per cent. With a similar interval of delay and penicillin in the amount of 200,000 units per kg., the survival rate was increased to 50 per cent. Results were essentially the same when the interval of delay in antibiotic injection was 1 hour. When the period of delay was increased to 2 hours, massive doses of penicillin were not effective. It appears, then, that best results are obtained by early injection of antibiotics. After short periods of delay, the survival rate may be improved by increasing the dose of antibiotics.<sup>16</sup>

**Open versus closed loop strangulation obstruction.** Survival time with and without antibiotics was compared in animals with open (30 cm.) and closed (10 cm.) loops of strangulated bowel. The best survival time (110 hours) was observed after

the administration of antibiotics to animals with open loop obstruction. When no antibiotics were given, the dogs with open loops survived for 90 hours. Animals with closed loops and antibiotics survived for 55 hours, whereas those which did not receive antibiotics lived 29 hours. It is probable that the survival period depends to a major extent upon the time of peritoneal exposure to bowel content. The open loop provides a route of decompression so that its contents leak into the peritoneal cavity later than in the case of the closed loop. The degree of improvement in survival time resulting from antibiotic administration was about the same in both groups.<sup>8</sup>

#### REMOVAL OF STRANGULATION FLUID

There seems to be little doubt that the dark peritoneal fluid of late strangulation obstruction, especially when lower levels of the gastrointestinal tract are involved, is toxic and poses a major threat to survival. Thorough removal of this material should thus comprise an integral part of the operative treatment of this condition. In order to evaluate the various methods of fluid removal, three groups of normal animals received intraperitoneal injections of strangulation fluid in the amount of 3 ml. per kg. In the first group the fluid was not removed, and the mean survival time was found to be about 12 hours. The fluid was removed from the peritoneal cavity of the animals in the second group by aspiration after 5 minutes of exposure. The mean survival time was about the same as that obtained for group 1. In the last group the peritoneal cavity was thoroughly irrigated with 1 L. of isotonic saline solution 5 minutes after injection of the toxic fluid. The mean survival time was 108 hours in the last group. In fact, four of these animals recovered completely. These findings suggest that irrigation of the peritoneal cavity provides the most effective method of removing the fluid.<sup>9</sup>

#### ANTIBIOTICS PLUS IRRIGATION

The efficacy of combining penicillin and irrigation in the management of animals after exposure to strangulation fluid was the concern of the following studies. The animals of group 1 received 5 ml. per kg. of strangulation fluid along with 600,000 units of penicillin, and there were no survivors. In group 2 the same amount of fluid was administered, but it was removed by irrigation of

the peritoneal cavity after 10 minutes. There were no survivors after the use of irrigation alone.

The next series involved the combined use of antibiotics and irrigation. When peritoneal exposure to fluid lasted for 10 minutes, all animals recovered. The same was true after 20 minutes of exposure, but as the interval was increased to 60 minutes, the survival rate dropped to approximately 40 per cent.<sup>8</sup>

Another study was carried out in which animals were exposed to their own strangulation fluid. The time of exposure was controlled by placing the segment of strangulated bowel in a plastic bag. At the appointed time the abdomen was opened, and a hole was made in the plastic bag, thus allowing the accumulated fluid to drain into the peritoneal cavity. Sixty per cent of the animals recovered when the method of treatment included antibiotics plus irrigation. There were no survivors when other methods of treatment were used.<sup>15</sup>

#### CLINICAL IMPLICATIONS

Although caution must be exercised in the transposition to patient care of data secured from experimental animals, it is thought that certain of the findings described above may gainfully influence the clinical management of strangulation obstruction and also possibly throw some light upon certain pitfalls which are responsible for the existing high mortality rate of this condition.

*Early operation.* Under existing circumstances, the key to successful management of the patient with strangulation obstruction is early operation. When the possible existence of the condition is suspected, every effort must be made to clarify the preoperative diagnosis and proceed with operation without delay. If operative intervention can be effected before peritoneal exposure to strangulation fluid has occurred, the chances for survival are tremendously increased. After exposure to the fluid has occurred, it appears that the shorter this period of exposure, the better the chances for survival. In certain difficult cases, the performance of a peritoneal tap with aspiration of bloody or dark red fluid has confirmed the diagnosis and prompted early operation. The removal of clear yellow fluid from the peritoneal cavity does not rule out impending strangulation. This procedure must be carried out with considerable caution in the presence of obstruction, but no serious complications have resulted from its use

in our experience. Other indications for immediate surgery in the obstructed patient include (1) continuous severe abdominal pain, (2) palpable abdominal mass, (3) rebound tenderness and (4) persistent shock after adequate replacement of fluids and electrolytes.<sup>3</sup>

*Preoperative preparation.* In addition to the administration of fluids, electrolytes, blood and nasogastric suction, the patient with strangulation obstruction should receive large amounts of antibiotics. The combination of penicillin and kanamycin was very effective in protecting experimental animals, and we prefer this combination for clinical use. Kanamycin (0.5 gm.) should be given intramuscularly when administered preoperatively. This antibiotic is capable of producing prolonged apnea when injected intravenously or intraperitoneally in the presence of various muscle relaxing agents which are commonly used by anesthesiologists. Experimental animals in shock from strangulation obstruction also have exhibited severe, irreversible hypotension as a result of intraperitoneal or intravenous injection of kanamycin. Damage to the eighth cranial nerve constitutes another known complication of kanamycin therapy. When a positive peritoneal tap is obtained, it is our practice to inject 1,000,000 units of penicillin into the peritoneal cavity before the needle is withdrawn. The discovery of a low white blood cell count in the presence of strangulation obstruction signifies peritoneal exposure to toxic fluid, in which case the prognosis must be guarded.

*Operative management.* A generous incision with ample exposure facilitates the rapid withdrawal of strangulated bowel from the peritoneal cavity. This should be followed by thorough aspiration of all free fluid, after which irrigation of the peritoneal cavity is carried out. Warm saline solution is used, and irrigation is continued until the solution is clear when aspirated. One million units of penicillin are left in the abdominal cavity after closure.

#### SUMMARY

The peritoneal fluid of late strangulation obstruction of the intestine is toxic and plays a major role in the lethal issue of this condition. Bacterial cells and probably endotoxins are largely responsible for the toxicity of this material. The toxicity of strangulation fluid increases from the upper to the lower levels of the gastro-

intestinal tract. Exposure to strangulation fluid results in the migration of large amounts of fluid into the peritoneal cavity. Antibiotics will protect normal animals against an otherwise lethal dose of strangulation fluid. As the dose of strangulation fluid increases, it is necessary to give larger amounts of antibiotics in order to provide protection. Delay in administration decreases the efficacy of antibiotics after exposure to strangulation fluid. The intraperitoneal route of antibiotic administration gave best results. Toxic fluid is most effectively removed from the peritoneal cavity by thorough irrigation. Best results were obtained with the combined use of antibiotics and peritoneal irrigation.

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## CARDIOPULMONARY TRANSPLANTATION: EXPERIMENTAL STUDY OF CURRENT PROBLEMS\*

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The extensive clinical success in replacement surgery indicates that transplantation and restoration of function is now possible in skin, cornea, bone, cartilage, fascia, blood vessels, tendon and even neonatal parathyroid<sup>14</sup> and thyroid tissues.<sup>19</sup> Furthermore, transplantation of a viable organ, such as the kidney, is possible if the donor is an identical twin<sup>11</sup> or a near relative whose minimal antigenicity has been overcome by massive body irradiation. As the immunologic problems of transplantation are solved, tissue and organ replacement will become an increasingly important part of our armamentarium for replacing damaged, malfunctioning or congenitally deformed structures.

Our laboratory now has several series of experiments on transplantation of the cardiopulmonary system. These procedures must remain experimental until further advances in overcoming the immunologic response are made. This paper presents our experiments on technical methods, on prolongation of the survival period of the recipient, and on prolongation of the survival period of the transplanted heart while the heart or lungs are maintained extracorporeally.

### IMMEDIATE TISSUE SURVIVAL

Early experiments demonstrated that the normothermic heart can survive total anoxia for at least 90 minutes without any evidence of damage and maintain physiologic work loads if the coronary capillary bed is protected from the formation of obstructing blood clots.<sup>22</sup> Crowell and Smith<sup>5</sup> prevented intravascular clotting by the use of either large doses of heparin or a fibrinolytic agent. This principle can also be utilized by removing all blood from the cardiac capillary bed by perfusion with an electrolyte solution. Later experiments<sup>23</sup> demonstrated that if the heart treated in this manner is refrigerated in a nutrient medium, it can be maintained at a temperature just

above freezing (4°C.) for at least 8 hours and again return to normal function. When maintained at 4°C. for longer periods of time, this preparation shows a steady deterioration of function after implantation by appropriate anastomoses to the neck vessels of a recipient animal according to the technique developed by Mann.<sup>15</sup>

The brilliant studies of Smith and Parkes<sup>18</sup> demonstrate that a tiny mass of tissue such as a slice of rat ovary can be frozen and maintained for over a year in liquid nitrogen (-190°C.). If larger masses of tissue can be deep-frozen in this way, it would seem only logical to deep-freeze organs. Barsamian and his coworkers<sup>2</sup> found that hearts can be chilled to -9°C. and restored to function when anastomosed to the neck vessels of the recipient animal. Their method of cooling with dehydration at reduced atmospheric pressure was the first to allow the temperature of an organ to be reduced below zero with successful restoration of function on warming. Since this method depresses rather than actually passes the freezing barrier, it has only limited practicability and does not allow for a significant extension of time, as they point out.

Further studies in our laboratory preliminary to passing the freezing barrier revealed little difficulty in cooling rat hearts to 1 or 2 degrees below 0°C. by perfusion with a chilled 15 per cent glycerol solution followed by warming on the Langendorff perfusion apparatus.<sup>25</sup> The lower temperature limit for liquid perfusion of the capillary bed is established by the fact that the glycerol electrolyte solution becomes too viscous below -5°C. Within the limits of applicability, this method would seem to be the ideal one for uniform cooling of an organ.

Jacob and coworkers<sup>12</sup> have utilized gaseous perfusion of the arterial circulation with helium chilled by liquid nitrogen to reduce the temperature of a kidney to -180°C. in 2½ hours. After the kidney had been warmed with warm helium, clear urinary filtration was possible for up to 2

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hours. External freezing by placing the insulated organ on a plate chilled with liquid nitrogen was less successful.

The ultimate solution for deep-freezing and storing large tissues may utilize the method of perfusion to achieve initial chilling, after which adequate time without tissue deterioration is available for achieving deep levels of freezing either rapidly or slowly, whichever may prove better.

Although glycerol is at this time the best agent for the slow freezing of all known tissues, it is toxic to normothermic but not to hypothermic tissues.<sup>13</sup> There is little doubt that better methods will be found to prevent intra- and extracellular crystal formation. Crystals may lead to the mechanical disruption of the cell and cellular membranes and to the denaturing of cellular proteins because of the excessive concentration of electrolytes and tissue solids as water is withdrawn by the formation of ice. The efficacy of the glycerol in protecting against freezing is related to the ability of each mole of glycerol to "bind" three moles of water, thus reducing, but not preventing, ice formation. This prevents excessive electrolyte concentration with its destructive effect within the cell.

It has seemed probable that warming does greater damage to an organ than freezing. Previously tried methods, except gaseous perfusion of the arterial system, have not transmitted heat uniformly throughout the tissues; they warmed the external surface to normal or higher than normal body temperatures while the center of an organ even as small as a rat heart might remain frozen. This allowed either deterioration or actual burning of the external tissue during thawing of the internal capillary bed.

#### PROBLEMS OF RECIPIENT MAINTENANCE

With the development of adequate pump oxygenators which are able to maintain extracorporeal circulation for a minimum of 1 hour at normal body temperatures, maintenance of the recipient animal became possible. Nonetheless, the use of profound hypothermia with or without the oxygenator would be of great value, since it would prevent diversion through the coronary and bronchial circulation of large amounts of blood requiring constant aspiration. The work of Gollan<sup>8</sup> demonstrated that a combination of the pump oxygenator with a heat exchange unit could

reduce body temperature approximately to the freezing level with survival of the animal on re-warming. More recently the work of Sealy and his coworkers<sup>18</sup> demonstrated that at 5°C. an animal could be maintained for at least an hour without any circulation and be restored to normal hemodynamics. Further work in our laboratory has confirmed this, and physiologic studies of both tissue and serum electrolytes<sup>9</sup> and of metabolism during this period have demonstrated that the physiologic alterations which occur are not extreme.

Trials in transplantation have included use of the method reported by Gordon, Meyer and Jones<sup>9</sup> which removes blood from the cavae, pumps it into the lungs *via* the pulmonary artery, and removes the oxygenated blood from the left atrium to be cooled and returned to the arterial system. Although this eliminates the oxygenator and is an excellent method of producing profound hypothermia, it does not seem applicable to cardiac transplantation, since the intracardiac tubing interferes with the anastomoses. In general, use of deep hypothermia combined with the pump oxygenator<sup>4</sup> appears to be the preferable system, since it eliminates pulmonary congestion from bronchial blood flow. With the diminished blood pressure, there is little or no tension on the suture lines during the performance of the anastomoses, and the bloodless field allows for a much more rapid technical achievement. The pump oxygenator system can be stopped during portions of the procedure in which a totally bloodless field is desirable and resumed during free intervals. This offers greater safety than the relatively unexplored arrest at near freezing temperatures. Since most of the procedure (original dissection, caval anastomoses, etc.) can easily be performed with circulation continuing, hypothermic arrest is not needed for long periods.

The studies of Gordon<sup>9</sup> and Sealy<sup>17</sup> and their associates demonstrate that the extremes of hypothermia may not be necessary during arrest; at 15°C. metabolic requirements have been reduced to nearly 10 per cent of normal with a corresponding extension of the time an animal can survive arrested circulation. This is nearly 1 hour, which in general is adequate for transplantation of the heart. Further depression of the temperature causes a less rapid fall in oxygen consumption and may not justify the deeper hypothermia. In addition, the heart usually stops beating between 19

and 15°C., increasing the ease of technical performance. Our studies to date indicate that this may be quite feasible for autologous or homologous transplantation.

#### TECHNICAL STUDIES IN CARDIOPULMONARY AUTOTRANSPLANTATION WITHOUT CARDIOPULMONARY BYPASS

In an attempt to produce a chronic study preparation, we have utilized autotransplantation of the heart and both lungs in the dog. To minimize the difficulties of this procedure, methods have been developed for its accomplishment without the use of the cardiopulmonary bypass which had been necessary in previous experiments.<sup>22</sup> This can be done only if extremely rapid anastomoses of the blood vessels can be performed serially without totally removing the heart and lungs from the body or interfering more than briefly with their continuing function. For this purpose, we have not found particularly satisfactory the vascular couples of Fryfogle<sup>7</sup> nor those that we have used in homologous cardiac transplantation.<sup>23</sup> In addition, stapling methods for vascular suturing by Androsoy<sup>1</sup> and Takaro<sup>21</sup> require more time than is feasible without cardiopulmonary bypass. Instead, the heart and lungs have been completely dissected free from all mediastinal attachments except the trachea, superior and inferior venae cavae, and aorta. Extreme care with hemostasis is mandatory; and freshly drawn, cross matched transfusions have been used to

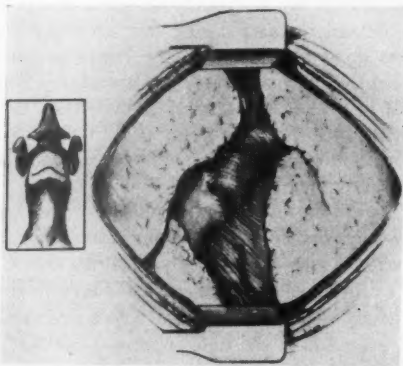


Fig. 1. Drawing showing incision. Much of the previous work has been done through longitudinal sternal splitting incisions, but the bilateral transverse thoracotomy through the fourth interspace offers a better exposure for the dissection and anastomoses of the atrial cuffs, pulmonary veins and trachea.



Fig. 2. Drawing showing coupling of aorta and venae cavae. The couple is more finely tapered at the ends than is indicated by the drawing. The knotted ligatures give multiple point fixation to prevent necrosis of the vessel wall.

maintain blood volume and a normal blood pressure at all times. The major vessels are serially divided and rejoined by nylon couples in the following manner. After inflow occlusion has been achieved and the heart has emptied, the aorta is partially transected and the plastic nylon couple inserted and tied in place with an ordinary heavy silk ligature. This can be performed usually within 90 seconds and rarely requires more than 2 minutes. After circulation has been re-established, transection of the vessel is completed. One of the cavae is then partially divided and coupled in similar fashion, while circulation continues through the other. The ligatures are then replaced by more distal ligatures of knotted heavy silk, as suggested by Rodriguez and Wofford,<sup>16</sup> to give multiple point fixation. These and various other experiments have demonstrated that such a method of anastomosis is compatible with long term vascular patency. The finely tooled couples with a smooth, inert interior do not appear subject to intravascular clotting.

The other major problem in cardiopulmonary transplantation has been the inability of these an-

imals with autotransplantation of both the heart and lungs to achieve normal respiration.<sup>10</sup> As previously described, the entire trachea can be divided with serial partial transection and suturing while respiration continues. It was our original hope that by leaving a long length of well innervated trachea by dividing it at the carina, sufficient afferent stimulation might be afforded to allow adequate pulmonary ventilation. Accordingly, in this series the trachea has been transected at the carina and immediately anastomosed, with care being taken to disturb as little as possible the tissues around the proximal trachea.

After the technical methods had been determined, four consecutive animals successfully underwent the total dissection and sequential division and reimplantation of the heart with both lungs. Each was able to return to the maintenance of a normal blood pressure and apparently normal cardiovascular function. Again, in spite of a well innervated lower tracheal segment, respiratory insufficiency was apparent in all, with none surviving longer than 14 hours.



Fig. 3. Drawing showing retraction of the heart and lungs for division of the trachea at the carina. With repeated partial transection and suture, adequate respiration can be maintained continuously without endobronchial catheterization.

#### RESPIRATORY INSUFFICIENCY

Faber and Beattie<sup>6</sup> suggested that pulmonary denervation might not be followed by respiratory paralysis, since they were able to demonstrate relatively normal spiograms in animals after excision and reimplantation of one lung and, 3 weeks later, a contralateral pneumonectomy. It is very significant, however, that their longest survival after the dual procedure was only 12 hours, as most died of "air hunger and anoxia." Some of our animals with various types of denervations have survived as long as a day, only to succumb to respiratory insufficiency. Thus, results of the experiments are similar, and the difference has been in the interpretation of "adequate," since neither group achieved continuing spontaneous respiration. The cardiopulmonary transplants produce a more extensive denervation of the respiratory tract, including the lower trachea, than denervation of only one lung as done by Faber, which leaves an innervated trachea, carina and a short segment of the left mainstem bronchus. The conclusion remains inescapable that continuing respiration is dependent on "feedback" afferents from the lower respiratory system.

Continued studies indicate that the paralysis is not due to phrenic nerve damage, excessive vagal or sympathetic dissections or periods of shock accompanying the extensive dissection and trauma of the actual transplantation.

For further evaluation of this point, four additional dogs were subjected to the preliminary dissection requisite for cardiopulmonary transplantation. The phrenic nerves were carefully dissected off the pericardium, and the vagal branches to the heart and lung were divided. The dissection was continued until only the trachea, aorta and venae cavae supported the heart and lungs. Extreme care was given to hemostasis, and the blood volume and arterial pressure were maintained with matched blood transfusions. The trachea was divided immediately proximal to the carina and anastomosed without interruption of ventilation at any time. At completion of this procedure, gentle mechanical stimulation of the phrenic nerves in the upper thorax above the sites of dissection demonstrated diaphragmatic responses. In addition, as the cough reflex was abolished, tracheostomies were performed for frequent endotracheal aspirations to prevent atelectasis from bleeding or retained secretions.

## RESULTS

Here again the results were comparable to previous experiments with denervation of both lungs and longer segments of the trachea. One dog was able to make only gasps during the early respiratory period, and the animal surviving longest breathed spontaneously for only 16 hours post-operatively. None, however, was able to maintain the continuing adequate ventilation necessary for permanent survival. Accordingly, it is the present conclusion that transplantation of the heart combined with both lungs is probably a physiologic impossibility.

Again attention is called to the possibility of transplantation of the heart with one lung. This has been demonstrated previously<sup>22</sup> to allow adequate pulmonary afferent stimulation from the remaining undisturbed lung and thereby be compatible with adequate respiratory efforts and prolonged existence. It does require extensive post-operative care for the denervated areflexic lung because of loss of the cough reflex.

At the present time, experimentation is proceeding on total autotransplantation of the heart to achieve a chronic preparation which will be suitable for physiologic study and on evaluation of the circulatory potentials of the transplanted denervated heart which has been subjected to extensive mechanical and thermal trauma.

## SUMMARY

The problems of cardiac and cardiopulmonary transplantation have been discussed, including the existing difficulties of freezing and thawing total organs.

A combination of the pump oxygenator and moderately profound hypothermia (10 to 15°C.) with intervals of total arrest assures a practical method of recipient maintenance and of technical ease for transplantation.

Simple techniques have been described for total cardiopulmonary autotransplantation without the use of hypothermia or the pump oxygenator.

Further experiments confirm the inability of an animal with denervation of its respiratory system distal to the tracheal carina to maintain adequate respiration, even with a tracheostomy to reduce dead space and to assure a clear tracheobronchial airway.

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## MEASUREMENT OF BLOOD FLOW THROUGH ISOLATED ORGANS: FURTHER EXPERIENCE WITH THE METHOD\*

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Measurement of blood flow continues to be a problem, in that no satisfactory, simple method has been devised that is not without some criticism. This is especially true of organ blood flow. Most methods involve incision of vessels and the introduction of suitable cannulas to conduct the blood to and from a measuring device or involve the insertion of a device directly into the lumen of the vessel in question. Other methods depend upon the extraction or elaboration of a substance by the organ.

There are obvious disadvantages to these methods. Cannulation introduces resistance to flow in addition to causing kinking and other artifacts. This difficulty is especially true in smaller vessels. Extraction or elaboration of a substance such as *p*-aminohippuric acid depends upon function, but function may not parallel blood flow. Anticoagulants must be used in cannulation, and this has been shown to influence vascular reactivity. For these reasons we devised the method reported previously.<sup>2</sup>

The effects of temporary arterial and venous occlusion in certain areas of the body have become important since the event of arterial reconstructive surgery. Vessels to be repaired must be clamped for varying lengths of time with resulting ischemia distal to the point of occlusion. Using the method described, we have measured blood flow in kidney and isolated segments of the intestine after varying modes and times of occlusion. Measurements of renal blood flow were obtained after infusions of norepinephrine and epinephrine into the blood stream. In addition, the effect of severe burns on renal blood flow was measured. The effect of heparin on blood flow after occlusion was assessed.

### METHODS

Adult mongrel dogs were anesthetized with pentobarbital, and midline laparotomy incisions

were made. Depending upon the study, either the left kidney or a segment of the ileum equidistant between the cecum and ligament of Treitz was dissected free from all attachments except its blood vessels. Blood supplies of the kidneys and intestinal segments were isolated and dissected free from enveloping mesentery and nerves for a distance of 3 to 7 cm. The intestinal segment was then isolated from the remainder of the intestine and suspended in a specially constructed aluminum pan supported by a Satham model G 1-8-350 displacement transducer. The kidney was suspended in a similar manner except that a nylon bag was used (fig. 1). In both cases, the height of the transducer was adjusted so that the artery and vein were horizontal. The transducer and recorder system (Sandborn 100 series) were calibrated so that 1 gm. of weight on the transducer would give 1 cm. of deflection on the recording system. The organs were then weighed by means of zero suppression. A suitable paper speed was selected and the vein to the organ suddenly occluded. Change in weight with time then should equal blood flow. Even if the rate of increase in weight decreases, by drawing a tangent to the curve at zero time (fig. 2), the rate of increase at zero time can be computed. Thus, any deleterious effect that clamping of the vein might have on the blood flow curve is masked.

By the method described above, control measurements of blood flow in kidneys and isolated segments of ileum were obtained. The vein was clamped for 30 minutes and measurements of flow obtained immediately after release of the venous clamp, and again 1 hour later. In another group the artery and vein were clamped for 1 hour; flow was measured immediately after, 1 hour after, and occasionally 2 hours after release of the clamp. In other animals the arteries to the organs being studied were clamped for 1 hour and flow measured immediately, 1 hour, and at 2-hour intervals after releasing the artery.

In six dogs, both the artery and veins to the organ in question were occluded after the injection of heparin solution (10 mg. per ml.). One

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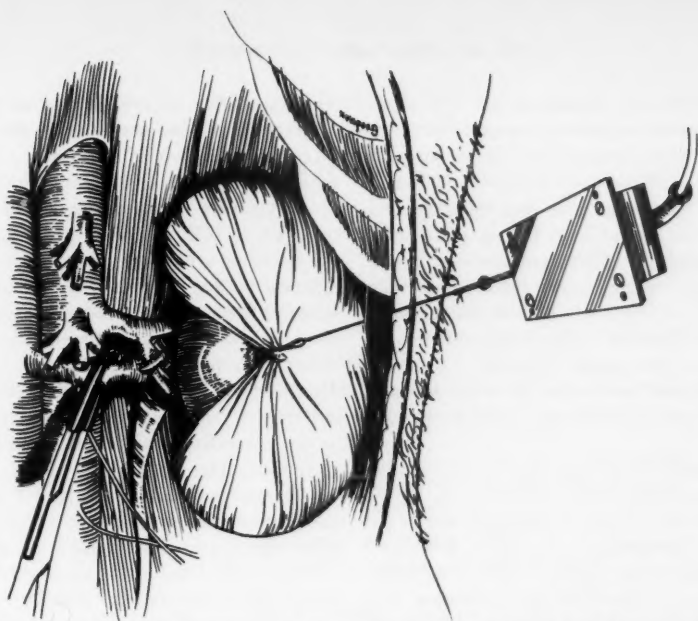


Fig. 1. The kidney can be seen suspended from the transducer. Normally the intestine is retracted. In this drawing the intestine has been removed to show the relationship of the vessels. If necessary, the ureter may be cut.

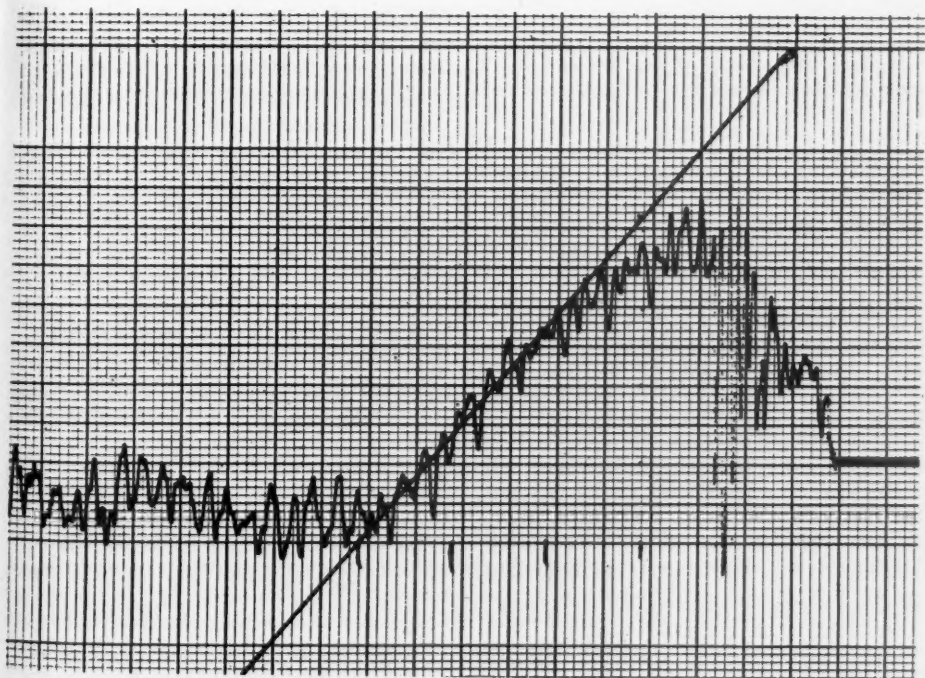


Fig. 2. This shows the progressive change in weight of the left kidney. The tangent is drawn parallel to the curve at zero time which is the point at which the weight curve rises. The slope of the tangent times paper speed in centimeters per minute, times the attenuator setting of the recorder, equals blood flow in milliliters per minute.

hour later, blood flow measurements were made as described in the preceding example.

Control measurements of renal blood flow, arterial pressure and resistance were obtained in 17 dogs. Ten of these dogs were then infused intravenously at the rate of 2  $\mu$ g. per kg. per minute with norepinephrine. Flow, pressure and resistance were measured again after the blood pressure stabilized. The norepinephrine was discontinued, and after stabilization of the blood pressure, the measurements were again repeated. Six of the dogs were studied in exactly the same manner, except that epinephrine instead of norepinephrine was used.

Control measurements of renal blood flow before burning were obtained in 17 animals. All the animals then received burns of 60 per cent of the body surface by immersion in water at 90°C. for 1 minute. Eight of the animals underwent determination of renal blood flow and resistance at 5, 15, 50 and 60 minutes after burning. The remainder of the group (nine animals) were treated identically except that heparin (2 mg. per kg.) was injected at the time of burning.

#### RESULTS

*Intestinal and renal blood flow.* Tables 1 and 2 show the composite results of the intestinal and

renal blood flow experiment. In all the animals subjected to venous occlusion for 30 minutes either of the kidney or of the intestine, there was a significant decrease in flow immediately and also at 1 hour after release. However, in the case of occlusion of both the renal artery and vein and the intestinal artery and vein, there was a marked difference in the reaction of the two organs. One-hour occlusion of the intestinal artery and vein produced no significant reduction in blood flow either immediately after release or 1 hour later. However, in the one-hour occlusion of the renal artery and vein, there was a significant decrease in flow immediately after and 1 hour after release of the occluding clamp.

One-hour occlusion of the intestinal artery did produce a significant decrease in flow immediately after release and also 1 hour later. One-hour occlusion of the renal artery alone caused a significant drop in blood flow immediately after release, but not so 1 hour after release. In table 3 may be seen the results of occlusion of the renal artery and vein after heparin had been injected into the renal artery. There was a significant reduction in renal blood flow immediately after release of the clamp and again at the end of 1 hour. The increase in renal resistance after restoration of flow was not significant; however, the increase in renal

TABLE 1  
*Renal blood flow\**

	Control	Immediately after Release	One Hr. after Release
	<i>ml./gm. tissue/min.</i>		
30-min. occlusion of renal vein.....	1.45	0.84( $P < 0.01$ )	0.85( $P < 0.05$ )
1-hr. occlusion of renal artery and vein.....	1.87	0.61( $P < 0.005$ )	0.56( $P < 0.001$ )
1-hr. occlusion of renal artery.....	1.66	0.72( $P < 0.005$ )	1.3( $P < 0.20$ )

\* Modified from Neely and Turner.<sup>3</sup> The figures given are the means of 9 or 10 animals in each group.

TABLE 2  
*Intestinal blood flow\**

	Control	Immediately after Release	One Hr. after Release
	<i>ml./gm. tissue/min.</i>		
30-minute occlusion of gut vein.....	0.27	0.07( $P < 0.005$ )	0.13( $P < 0.005$ )
1-hr. occlusion of gut artery and vein.....	0.26	0.27( $P < 0.80$ )	0.17( $P < 0.10$ )
1-hr. occlusion of gut artery.....	0.40	0.21( $P < 0.01$ )	0.22( $P < 0.01$ )

\* Modified from Turner, Neely and Barnett.<sup>4</sup> The figures given are the means of 9 or 10 animals in each group.

TABLE 3

*Effect of heparin on renal blood flow after simultaneous artery and vein occlusion for 1 hour\**

	Control	Immediately After Release	One Hr. After Release
Blood flow (ml./min.).....	134	68 ( $P < 0.025$ )	36 ( $P < 0.05$ )
Blood pressure (mm. Hg).....	100	100	90
Resistance (arbitrary units).....	1.58	3.94 ( $P < 0.10$ )	4.59 ( $P < 0.02$ )

\* The figures given are the means of 6 dogs.

TABLE 4

*Results of infusion of epinephrine and norepinephrine on renal blood flow, blood pressure and renal resistance to blood flow in dogs\**

	Norepinephrine†			Epinephrine†		
	Control	During	After	Control	During	After
Flow (ml./min.).....	132	73 ( $P < 0.01$ )	116	158	83 ( $P < 0.02$ )	186
Pressure (mm. Hg).....	118	171	109	99	181	92
Resistance (arbitrary units).....	1.03	2.99 ( $P < 0.005$ )	1.13	0.80	2.59 ( $P < 0.005$ )	0.58

\* Infusion at the rate of 2  $\mu$ g. per kg. per minute in the femoral vein.

† The figures given for norepinephrine are the means of 10 dogs; for epinephrine, of 7 dogs.

resistance 1 hour after release of the clamp was significant.

*Effect of norepinephrine and epinephrine on renal blood flow.* The infusion of epinephrine and norepinephrine into the intact animal caused a significant decrease in renal blood flow and also a significant increase in renal resistance (table 4). A remarkable finding in this group of animals was the fact that in some of the epinephrine treated animals, discontinuance of the epinephrine was followed by a rise in blood flow of 300 per cent above control values.

*Effect of heparin on renal resistance after burning.* Table 5 shows the results of the burn experiment. In 1 hour, with or without heparin, a marked increase in resistance occurred.

## DISCUSSION

There is an apparent paradox between the effect of occlusion of blood flow to the kidney and the intestine. Renal blood flow was still significantly reduced by occlusion of the artery and vein at the end of 1 hour after release of the clamps. Occlusion of the artery alone for 1 hour produced no significant reduction in flow as measured 1 hour after release of the clamps.<sup>3</sup>

However, occlusion of the intestinal artery and vein for 1 hour produced no significant reduction in flow immediately or at the end of 1 hour. Occlu-

TABLE 5

*Renal resistance after burns of 60 per cent of body surface\**

	Before Burns	After Burns			
		5 min.	15 min.	30 min.	60 min.
Without heparin (8 dogs)...	1.02	1.40	1.72	1.71	4.64
With heparin (9 dogs).....	1.13	1.59	1.55	1.90	4.19

\* Data from work in progress performed by the authors in conjunction with Byron E. Green, M.D. and C. P. Artz, M.D.

sion of the artery for 1 hour resulted in a decreased blood flow immediately after release of the clamp and 1 hour later.<sup>4</sup> The question is raised as to why the vascular bed in one organ reacts differently from that in another. In renal artery and vein occlusion, one might postulate that blood was trapped within the vascular tree and that intravascular thrombosis developed. Arterial occlusion alone allowed the blood to drain out, thus minimizing thrombosis. Whatever the cause, occlusion of both the artery and vein of the intestine produced the opposite effect. It appears that entrapped blood may hold the intestinal vascular system open.

Although it is well known that reactive hyperemia follows hypoxia and short term vascular occlusion, no hyperemia was observed in long term occlusion periods in this study.

To assess the effect of anticoagulants in preventing the decrease in blood flow after occlusion of the renal artery and vein, heparin was injected into the renal artery after occlusion of the renal artery. The renal vein was then occluded. As can be seen from the results in table 3, heparin appeared to have no effect on the resulting increased renal resistance after occlusion of the artery and vein. Thus, some factor other than intravascular thrombosis must be operating to cause this phenomenon.

The view that thrombosis is not a factor in causing increased renal resistance was confirmed in the heparin-burn experiment. As can be seen from the data, the heparin had no effect on the renal vascular resistance after burning. However, this does not establish that heparin may not be efficacious in the treatment of burns. It may be that the initial increase in renal resistance is due solely to the increase in blood viscosity caused by the rise in hematocrit. Intravascular thrombosis may influence flow later. In this case, heparin would prove beneficial. Further studies to test this aspect of the problem are contemplated.

Epinephrine and norepinephrine cause preferential vasoconstriction of the renal vascular bed, as manifested by the increase in resistance. At first glance, this is somewhat at variance with Guyton's<sup>1</sup> concept of total circulatory pressure. In our study, however, the kidneys were not connected to the sympathetic nervous system. They reacted then with humoral control only, whereas the remainder of the vascular bed remained under integrative nervous control.

The increase in flow in some animals after the discontinuance of epinephrine is probably a manifestation of the dilator property of epinephrine.<sup>5</sup>

#### SUMMARY AND CONCLUSIONS

1. Further experience with a dependable method of measuring organ blood flow is presented.
2. The principle upon which the method is based is a modification of the plethysmographic method.
3. Reactivity of the vascular bed differs in intestine and kidney. Heparin does not alter this reactivity.
4. Heparin does not alter the reactivity of the renal vascular bed after severe burns.
5. Epinephrine and norepinephrine are capable of increasing renal resistance tremendously even in nonbled animals. Epinephrine causes a paradoxical decrease in some animals after the discontinuance of the drug.

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## MITRAL COMMISSUROTOMY\*

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The modern operation for mitral stenosis has been performed in many centers throughout the world and several series of cases have been analyzed.<sup>1, 3, 4, 6, 7, 8, 9, 10</sup> Sufficient experience has been obtained to discuss the special problems in selection of patients, diagnosis, surgical technique and prognosis. This paper is based on experiences obtained with 38 cases including 25 cases discussed in a previous paper.<sup>9</sup> It is the purpose of this paper to make a brief statistical analysis of this group of patients and to discuss in more detail some of the special problems that have arisen during their management.

The thoracic surgeon should have the services of a cardiologist both for aid in selection of patients and the management of certain complications peculiar to these cases, such as arrhythmia and congestive heart failure, which may arise during the postoperative period. In handling this series of cases, teamwork has been emphasized, the team consisting of the surgeon, cardiologist and anesthesiologist. The 38 cases reviewed in this series were operated on between December of 1952, and March of 1960, and consisted of 21 women and 17 men. These patients varied in age from 18 to 56 years. The age distribution is given in table 1. Twenty-six cases were between 22 and 40 years. It is interesting to note that all patients in this series were white, even though the state's population is about 45 per cent Negro. Mitral stenosis is not commonly found in the Negro race.

TABLE 1  
*Age of patients*

Age	Number
18	2
22-30	10
31-40	16
41-50	7
51-56	3

\* From the Department of Surgery of the University of Mississippi Medical Center, Jackson, Mississippi.

Most patients gave a history of significant symptoms from 1 to 5 years' duration. Two had had such symptoms for less than 2 years and 10 for more than 5 years. The average patient gave a history of progressive dyspnea and fatigue on exertion. Many experienced hemoptysis, and a few noted this at the onset. Six patients gave a definitive history of preoperative emboli. Twenty-five of the 38 cases gave a history of rheumatic fever in childhood.

### DIAGNOSIS

The diagnosis was not a difficult problem in most cases. There were two types of cases encountered, pure mitral stenosis and mitral stenosis combined with mitral regurgitation or aortic valvular disease. The pure mitral stenosis has a loud snapping quality to the first sound at the apex. An "opening snap" is also heard at the apex. There may be a faint systolic murmur of grade I or II intensity. A classic diastolic murmur presystolic in accentuation is heard in those cases with normal sinus rhythm. Usually the pulmonary second sound is increased and a Graham-Steele type of murmur may be present.

In cases with mitral stenosis and regurgitation, a grade III apical systolic murmur is also heard. In cases of mitral stenosis and either aortic stenosis or aortic insufficiency, the characteristic murmur of these lesions in the aortic valve area is heard.

Thirteen of the 38 cases had auricular fibrillation.

The chest roentgenogram with barium swallow revealed an enlarged left atrium and pulmonary artery in every case (figs. 1 and 2). Calcium could be visualized at fluoroscopy in the mitral valve area in those patients with appreciable calcification.

In one case there was marked enlargement of the left pulmonary artery (fig. 2), causing the cardiologist to consider the possibility of an associated left to right shunt. This patient was one of the few who had cardiac catheterization before



FIG. 1. A. Posteroanterior view of chest in an 18-year-old female with mitral stenosis. Note enlargement of the pulmonary artery and the atrium at the site of the arrows. B. Right anterior oblique view of chest in same patient with barium swallow to illustrate enlarged left atrium.

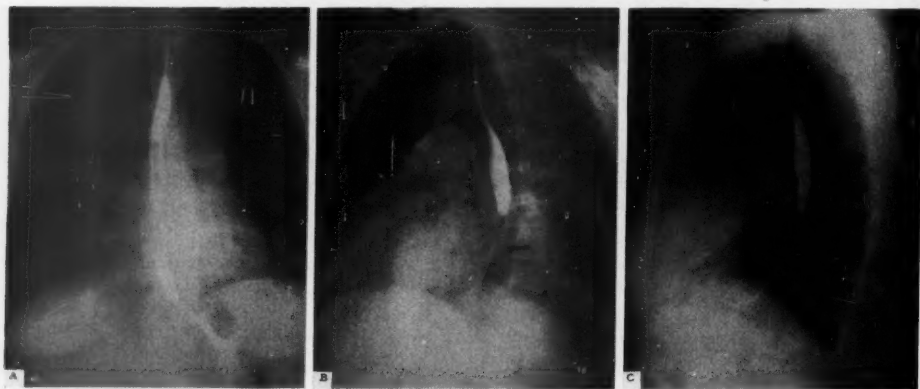


FIG. 2. A. Posteroanterior roentgenogram of chest in a 43-year-old female with mitral stenosis. Note marked enlargement of the pulmonary artery. B. Right anterior oblique view in the same patient. C. Lateral view in same patient. Note enlargement of left atrium.

surgery in this series. The pressure in the right atrium was 13/3 mm. Hg; in the right ventricle, 138/7 mm. Hg; and in the pulmonary artery, 138/50 mm. Hg. At the same time, the pressure in the brachial artery was 140/94 mm. Hg. Arterial oxygen saturation studies revealed no evidence of a shunt. At surgery this patient had a tight mitral stenosis with no other lesions. The pulmonary artery was the largest seen in this series of cases. All patients that were explored were found to have mitral stenosis.

#### SELECTION OF PATIENTS

All patients selected were symptomatic. The presence of mitral regurgitation and other valvular defects has not been considered a contraindication for surgery so long as mitral stenosis was the dominant lesion. In fact, one of the best results obtained in this series was in a patient who had moderately severe mitral regurgitation. He is still very active 7 years after surgery. Patients with mitral stenosis and regurgitation should have

electrocardiographic evidence of right axis strain or deviation before being considered for mitral commissurotomy.

Two patients were selected for surgery who were pregnant; the cardiologist did not think that they could go through pregnancy without surgery. Surgery was performed in each case during the 4th month of gestation. These patients tolerated surgery and pregnancy well, but did not appear to have as much improvement in exercise tolerance in the immediate postoperative period as the average patient. They improved much more rapidly after delivery.

#### DIGITALIZATION

Most patients have been of necessity digitalized at some time before surgical consultation. For the few patients who have not required digitalization but who have sufficient curtailment of exercise tolerance to justify surgery, digitalization has been recommended before surgery. About 25 per cent of the patients with a normal sinus rhythm will develop auricular fibrillation for a varying period of time postoperatively. Without preoperative digitalization, this may present a medical emergency in the postoperative period, but with digitalization the ventricular rate is kept within safe limits even in the presence of a sudden onset of auricular fibrillation. With digitalization the patient's myocardium can better tolerate the stress, strain and trauma of the surgical procedure.

#### ANESTHESIA

Premedication should be light to moderate. The dose of atropine is determined by the pulse rate, which should be kept below 100 per minute before induction. Meticulous attention must be paid to assure light anesthesia, high percentage of oxygen, and more than usual ventilation. Cyclopropane was frequently used at first with patients who had a normal sinus rhythm. It soon became evident that the myocardium was much more irritable under this agent than under ether. This was particularly noted while the purse string was being placed about the auricular appendage and while the commissure was being opened. One patient with auricular fibrillation was given 150 mg. of Surital, and a succinyl-choline chloride drip was used for intubation. Cyclopropane was then given, and the blood pressure fell rapidly and car-

diac activity ceased. An emergency thoracotomy was done almost immediately, and the heart was found at a complete standstill. After a brief period of cardiac massage, the ventricles began to fibrillate. The defibrillator was used with success, and normal ventricular contractions were resumed for only a minute or two. During massage the tip of the auricular appendage was removed, and a finger fracture commissurotomy was performed. Massage was continued for 1½ hours without success. Apparently cyclopropane precipitated ventricular fibrillation in this patient who already had auricular fibrillation.

After 15 to 20 minutes of ventilation with oxygen, patients are now induced with Pentothal sodium and carried during the operation on ether. A very light anesthetic state is maintained, the patients often responding to stimuli during surgery. Consciousness is regained a few minutes after the operation is completed, as a rule.

Fluid replacement during surgery must be very closely regulated. Thirteen-gauge needles are used intravenously, and blood is replaced in amounts equal to that lost moment by moment. The amount required in these cases varies from 300 to 1500 ml. each. Care is taken to give only the minimal amount of infusion solution necessary to keep the cannulae open.

Postoperatively the head of the bed is elevated to reduce gravitational congestion and edema. Frequent carbon dioxide inhalations—pure carbon dioxide is delivered into the cupped hand over the nose and mouth for 15 to 20 seconds or five or six breaths—are used to produce marked hyperventilation, coughing, toning and desirable activity, especially in those patients who refuse to perform such activity voluntarily. Oxygen is continued, usually by nasal catheter, for the first day or two after surgery.

#### TECHNICAL PROBLEMS

The left posterolateral approach has been used in all cases, and the incision is made through the fourth intercostal space. A purse string has been used about the auricular appendage and the atrial cavity entered after excision of the tip of the auricular appendage. A finger-fracture technique was adequate in most cases. The anterolateral commissure has been opened in every case, either with or without the use of a knife. This commissure is very accessible when ap-

proached through the left auricular appendage. The flexed index finger can be placed deep into the commissure and anterior pressure exerted while counterpressure is being placed on the heart with the left hand. If the commissure does not fracture with a reasonable amount of pressure, a knife should be used. Usually the valve leaflets are more densely adherent near the opening than further toward the annulus. Once the commissurotomy is started with or without a knife, the anterolateral commissure can be opened well out to the heart wall. This should be accomplished slowly. If at any time it becomes evident that regurgitation is being produced, the commissurotomy should be stopped. The greatest obstacle to accomplishing an adequate opening of this commissure is heavy plaques of calcium which sometimes render the procedure quite difficult. There were nine patients in this series who had marked calcification of the valve leaflets. The leaflets were very difficult to separate and were not very mobile even after some separation had been accomplished in these cases.

The posteromedial commissure is not nearly as accessible and is much more difficult to open. Almost the entire finger must be inserted into the atrial cavity to encounter this commissure adequately. The finger is pushed posteromedially. One cannot flex the finger under the commissure or apply counterpressure; a counterclockwise motion of the finger will sometimes fracture this commissure. This commissure moves about while being manipulated, which makes the maneuver more difficult. Most knives cannot be used with any degree of accuracy on this commissure, but the Bakst fingernail knife<sup>2</sup> can be accurately placed by palpation and is fairly effective. If possible, this commissure should be completely opened. Harken<sup>7</sup> has stated that this commissure can be opened better if the surgeon stands on the right side of the table. Beck<sup>5</sup> has enlarged the index finger by wrapping umbilical tape about it and covering this with a second glove. This enlargement of the finger may fracture the posteromedial commissure, but this technique requires a large auricular appendage which is not present in many cases. The posteromedial commissure, with its proximity to the aortic valve and its inaccessible position and inability of the surgeon to apply counterpressure, presents one of the greatest technical problems in this operation. The best

results will be obtained only when both commissures are opened adequately.

The atrial wall was inadvertently torn three times in this series of cases. In one patient the auricular wall was torn in a radial fashion from the opening in the auricular appendage. This was probably produced by the dilating effect of the index finger. In the other two patients the tear was at the atrioventricular sulcus. In one case, the index finger slipped over the anterolateral commissure during finger-fracture commissurotomy perforating the atrial wall. This presented a very precarious and alarming situation. As long as the finger plugged both holes in the atrial wall, there was very little if any bleeding. In the other case, the tear in the same area was produced when the surgeon inadvertently tugged on the purse string with his flexed middle finger while fracturing the posteromedial commissure. With the tip of the index finger placed against the torn area from inside, the atrial wall bleeding was controlled. In each case the surgeon was able to place a row of interrupted 3-0 silk sutures with his left hand while the right index finger in the atrium was used to control bleeding and to guide the needle. There was minimal bleeding in each case, but it would have been considerable had the index finger been removed from the atrium in order to repair the lacerations. The commissurotomy was then completed, the auricular appendage closed, and the appendage was flexed toward the ventricle and sutured to the ventricular wall to provide additional protection against hemorrhage. There was no postoperative hemorrhage from the heart in these or any other cases in this series.

Subvalvular stenosis was encountered in three advanced cases. The adherent chordae tendineae and papillary muscles could be separated to a certain extent by finger manipulation.

Clots were encountered in the auricular appendage in five patients. One was a large organized thrombus densely adherent to the atrial wall. It was left in place, and the index finger could be worked by the thrombus and a good finger-fracture commissurotomy performed. The other clots were removed. During manipulation, the anesthesiologist compressed the carotid vessels. This was not effective in preventing cerebral emboli in two cases. In one patient, homonymous hemianopia was produced and in the other patient, multiple cerebral, renal and cardiac emboli were produced.

There were emboli in two other patients, one to

the left kidney and the other to the left popliteal artery. It was interesting to note that a few seconds after commissurotomy in the second case above, the anesthesiologist reported that the arterial pulse was absent in the right upper extremity and present in the left. In a few seconds it returned to the right upper extremity. After operation the patient was found to have a cold left foot and leg with normal left femoral pulsations. Apparently this clot temporarily plugged the right innominate artery and was later carried to the lower extremity. This embolization was treated with lumbar sympathetic block and an intra-arterial drip of fibrinolysin. Pulsations did not return to the left foot with the use of fibrinolysin, as was hoped, but the extremity remained viable and was asymptomatic after 2 weeks.

Care was taken to avoid valve cusp damage and to prevent the production of mitral regurgitation in every case. Significant mitral regurgitation was only produced in one patient. A finger-fracture commissurotomy was performed in this case with very little pressure, and the exact cause of the regurgitation was not clear. This patient was clinically improved by the operation and has remained improved for  $2\frac{1}{2}$  years after surgery. Even though she has mitral regurgitation of moderate degree, there has been no appreciable cardiac enlargement.

There was marked calcification of the valve in nine patients, moderate calcification in four patients, and no calcification in 20. One patient died during induction of anesthesia and is not included.

#### POSTOPERATIVE COMPLICATION

Several patients had transient episodes of auricular fibrillation during the 1st week postoperatively, but it persisted in two cases. One patient returned 7 weeks postoperatively because of auricular flutter. It was converted to a regular sinus rhythm with quinidine. During the postoperative period, four patients developed left chest pain, pericardial friction rub and fever. One patient had five attacks from 2 to 19 months postoperatively. The more severe attacks were treated successfully with steroid therapy. One mild attack was treated with salicylates, and relief was obtained.

Pulmonary atelectasis was encountered in three patients. Two responded to expectorants, tracheobronchial suction and coughing, but the other patient required bronchoscopy on two occasions before the collapsed right lower lobe would expand. There was typical reactivation of

rheumatic fever in a 32-year-old female patient. She developed fever and hot red swollen joints and did not improve after surgery. The other severe complications were bleeding from pre-existing duodenal ulcer one patient, mild wound infection one patient, and transient postoperative psychosis one patient.

Two patients developed subacute bacterial endocarditis months after surgery, one, 18 months after surgery and the other, 32 months after surgery. Both cases were successfully treated by massive doses of intravenous penicillin.

#### DEATHS

There were three operative deaths. One patient died during induction of anesthesia and apparently developed auricular fibrillation. The second death occurred 36 hours after surgery in a 56-year-old patient with marked chronic arteriolonephrosclerosis, left renal infarction and liver changes secondary to chronic passive congestion. The third death was that of a 42-year-old male patient who experienced multiple emboli involving the brain, myocardium and kidney at the time of surgery. He later developed endocarditis, staphylococcal pneumonia and empyema. He died on the 7th postoperative day. There have been six late deaths. Two of these were not related to the disease. Both these patients had definitely improved as a result of surgery. One died 4 years and 10 months after surgery with a bleeding duodenal ulcer. The other died 3 years and 9 months after surgery with carcinoma of the cecum with metastases. The other four late deaths were due to progression of the disease. They died 5 months, 2 years, 2 years 3 months, and 3 years 6 months after surgery. Three of the four late deaths had moderate to marked calcification of the valve leaflets. The fourth patient was a 54-year old man who had had symptoms for 11 years. He had auricular fibrillation, multiple preoperative emboli, a large clot in his left atrium and mitral regurgitation of moderate degree.

#### RESULTS

The results of 23 patients, 66 per cent of those who survived surgery, have been classified as excellent. There were eight additional cases that were significantly improved, 23 per cent of those surviving surgery. Of these eight, recurrences were experienced by two, one of whom died  $3\frac{1}{2}$  years after surgery. The other had a recurrence 7 years postoperatively and will probably require



reoperation. Four patients were unimproved. This gave a total of 89 per cent improvement among the survivors of the operation. There were three operative deaths.

As has been pointed out by Ellis and associates, (6) the principal factor preventing a good result was extensive calcification of the valve. Of the nine patients in this series whose valve leaflets were markedly calcified, only three are improved over their preoperative state now. One is living and unimproved at present. The remaining five patients are dead, two operative deaths and three late deaths. It is not believed that the slight mitral regurgitation that was present in six of these cases was an important factor in the poor results. If these nine patients with marked calcification were removed from the series, the results would be greatly improved, with only one operative death and one late death. The presence of calcification as determined at fluoroscopy does not necessarily mean calcification of this extent, and it is difficult if not impossible to determine the degree of calcification.

If marked calcification and fixation of the valvular structure could be determined preoperatively, it would probably be advisable to plan an open operation for this group, with the realization that some of these patients cannot be helped even by the open technique.<sup>10</sup> The average case of mitral stenosis should be corrected by the closed technique.

Another finding which gives a poorer than average prognosis is auricular fibrillation. This generally is an indication of advanced disease. Only five of the thirteen patients with auricular fibrillation obtained an excellent result and one obtained significant improvement. All the operative deaths and three of the four late deaths due to progression of disease were in this group. One patient of this group is living in an unimproved condition. In general, the older patients did not respond as well as the younger.

There were 20 patients under 45 years of age who had a normal sinus rhythm and only moderate calcification or less of the mitral valve; 16 obtained excellent results and three others were significantly improved; thus 95 per cent of these patients were improved. There was only one unimproved patient in this group, this result being due to rheumatic activity. There were no operative or late deaths due to cardiac disease in this group.

#### SUMMARY

1. Mitral commissurotomy was performed on 38 patients with mitral stenosis. The problems of diagnosis, selection of patients and anesthesia, and certain technical problems have been discussed.

2. There were three operative deaths. Eighty-eight per cent of the survivors were definitely improved. There were four late deaths due to progression of the disease.

3. Marked calcification of the valve leaflets was the greatest obstacle to a good result. Other factors that mitigated a good result were auricular fibrillation and age.

4. Of the 20 patients under 45 years of age who had a normal sinus rhythm and moderate or less than moderate calcification of the valve leaflets, 19 were improved. The one unimproved patient developed rheumatic activity after surgery.

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## THE STAPHYLOCOCCAL PROBLEM: CURRENT TRENDS IN CONCEPTS AND MANAGEMENT\*

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During the past century, the introduction of aseptic surgery and the discovery of potent antibiotics have done much to combat the action of staphylococci as agents of disease. However, while man has discovered new and more powerful chemotherapeutic agents against these organisms, the staphylococci have developed resistance, or strains resistant to current antibiotic therapy have arisen.

Increased emphasis has been placed on staphylococcal infections within the past few years because strains resistant to the commonly used antibiotics have become disseminated throughout hospitals and, in some instances, to the general population. In addition, more patients particularly susceptible to infection enter the hospital environment where they are available for attack by resistant forms of staphylococci.

For the past 3 years, the Surgical Bacteriological Laboratory at the University of Mississippi Medical Center has been conducting environmental, clinical and laboratory studies on the staphylococcal problem. These studies and a discussion of their implications are presented in the hope that, with the fast growing body of similar studies being carried out in many hospitals, they may bring help to clarify the staphylococcal problem and its solution.

### TRENDS IN SENSITIVITY OF STAPHYLOCOCCI ISOLATED FROM PATIENTS

During 1959, 1308 cultures of coagulase positive *Staphylococcus aureus* were seen in the clinical laboratory of this hospital. These organisms were tested by the sensitivity disc method and were phage typed (table 1). Sixty-five per cent of the organisms were resistant to penicillin, 1.2 per cent resistant to novobiocin, and 34 per cent resistant to chloramphenicol. During the first 5 months of 1960, 716 cultures of *S. aureus* from patients were seen in the laboratory. There was evidence of increased resistance (80

per cent to penicillin, 18 per cent to novobiocin, 51 per cent to chloramphenicol). The number of phage type 80/81 increased from 50 per cent in 1959 to 58 per cent in 1960. Almost all staphylococcal organisms during this period of study were sensitive to kanamycin and vancomycin, which are rarely used in the hospital except in overwhelming or particularly resistant infections. Chloramphenicol has been used increasingly during the last 2 years.

### SENSITIVITY PATTERN OF PHAGE TYPE 80/81 STAPHYLOCOCCUS AUREUS

The most common strain of *S. aureus* in most hospitals is phage type 80/81. In an attempt to study its sensitivity pattern, 418 strains of 80/81 *S. aureus* were compared with 298 strains isolated from patients within the hospital who were not of the 80/81 type (table 2). It was apparent that organisms of the 80/81 strain were much more resistant to all antibiotics except kanamycin and vancomycin than were the other strains of staphylococci.

### STUDIES OF NOSE AND THROAT CULTURES

One of the most important sources of staphylococci was the nose and throat of patients and personnel. In order to study the staphylococcal flora of noses and throats, a rather extensive survey was carried out (table 3). Of 150 individuals working in the hospital, 53 per cent carried coagulase positive *S. aureus* in their noses or throats; 29 per cent carried phage type 80/81. In 184 patients who were studied at the time of admission, 44 per cent showed the presence of coagulase positive staphylococcus in their noses or throats, but only 6 per cent were positive for phage type 80/81.

In an attempt to obtain more information concerning the carrier rate in the general population, a statistical planned survey was made of Jackson, Mississippi (population 130,000) in which the noses and throats of 1640 individuals were sampled. There were 37 per cent who were

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TABLE 1

*Trends in sensitivity of staphylococcus isolated from patients\**

Time	No. of Staph Cultures	Penicillin	Tetracycline	Streptomycin	Novobiocin	Bacitracin	Chloramphenicol	Erythromycin	Kanamycin	Vancomycin	Per cent 80/81†
Jan. 1, 1959–Dec. 31, 1959	1308	65	58	59	1.2	2	34	39			50
Jan. 1960	157	75	67	68	0		46	42			62
Feb.	137	86	65	94	19	39	67	49			54
March	155	83	65	93	13		45	43	1		58
April	138	80	58	96	11		52	46	2	0	52
May	129	74	61	89	28		45	52	1	0	63
Average 1960	716	80	63	88	18	39	51	46	1	0	58

\* Sensitivity is given as percentage of resistance.

† 80/81 = Strains lysed by 80/81, 52/80, 52/52A/ 79/80/81.

TABLE 2

*Comparison of sensitivities of 80/81 staphylococci and of other types (1960)*

Type of Organism	No. of Cultures	Per cent Resistant to.								
		Penicillin	Tetracycline	Streptomycin	Novobiocin	Bacitracin	Chloramphenicol	Erythromycin	Kanamycin	Vancomycin
Staphylococci 80/81.....	418	96	95	96	26	11	69	72	1	0.2
Staphylococci other than 80/81.....	298	56	17	80	3	33	22	12	1	0.4

TABLE 3

*Summary of nose and throat cultures from patients, hospital personnel and subjects in the community*

Category	Number	Per cent with Coagulase Positive Staph	Per cent with 80/81	Penicillin	Tetracycline	Bacitracin	Chloramphenicol	Erythromycin	Oleandomycin	Kanamycin	Vancomycin
Hospital personnel.	150	53	29	55	33						
Hospital patients on admission.....	184	44	6	17	6	1	4	5	4	0	0
Subjects from the community.....	1640	37	4	29	9		7	7			

positive for coagulase positive staphylococci, but phage type 80/81 was found in only 4 per cent.

From this study it would appear that a large percentage of hospital personnel are carriers of staphylococci and that an appreciable number carry the 80/81 phage type. Although about one-third of the individuals within the community carry coagulase positive staphylococci in their noses or throats, only a few show phage

type 80/81. Likewise, few patients on admission to the hospital carry an 80/81 organism in their noses or throats.

To determine the number of patients who became carriers of staphylococci during their stay in the hospital, a survey was conducted on 184 patients from the medical and surgical wards (table 4). On admission, 44 per cent carried coagulase positive staphylococci and 6 per cent, phage type 80/81. During the time in the hos-

TABLE 4

Summary of nose and throat cultures on hospital patients at time of admission and discharge\*

	Admission	Discharge
% Patients with coagulase positive culture...	44	56†
Phage type 80/81.....	6	9†
% Resistance to antibiotic		
Penicillin.....	17	25
Tetracycline.....	6	9
Novobiocin.....	1	3
Chloromycetin.....	4	7
Erythromycin.....	5	9
Vancomycin.....	0	0
Kanamycin.....	0	0
Oleandomycin.....	4	9

\* Data from 184 patients, 75 from medical wards and 109 from surgical wards.

† Twelve per cent developed coagulase positive cultures in the hospital. Three per cent developed phage type 80/81 in the hospital.

pital, which averaged 9 days, an additional 12 per cent developed coagulase positive staphylococci in their noses and throats, whereas an additional 3 per cent became carriers of the 80/81 phage type. There was a slight increase in the antibiotic resistant patterns of the organisms at the time of discharge in comparison to the patterns on admission. No comparison was made between patients who received antibiotics and those who did not. In a more precise study, Knight<sup>5</sup> found that the carrier rates of coagulase positive staphylococci in nose cultures showed a slight increase during hospitalization. The increase occurred in patients given antibacterial drugs and in those who were untreated.

#### STUDIES OF STAPHYLOCOCCI IN VARIOUS AREAS OF THE HOSPITAL

Cultures from various areas of the ward section of the hospital were taken on two occasions (table 5). Coagulase positive staphylococci were found to be present in many ward areas, including clean beds, the food tables and the dressing cart. A moderate number of phage type 80/81 was found. That coagulase positive staphylococci inhabit all areas of the hospital is obvious from this small survey.

In an attempt to find the number of organisms present at various times in the operating room,

TABLE 5

Staphylococci in various ward areas of the hospital

Area of Culture	No. of Cultures	Staphylococci		Phage Types of Coagulase Positive Organisms	
		Coagulase Positive	Coagulase Negative	No.	Type
Wash areas	20	6	17	5	80/81
				1	Va4/53/77
Clean beds	5	3	3	1	Nontypable
				1	80/81
				1	Va4/53/77
Soap	6	0	1		
Drinking water	7	0	4		
Food table	8	6	6	1	Va4/6/47C/54
				3	80/81
				1	Va4/47/53/77
				1	Nontypable
Dressing cart	7	2	4	2	Nontypable
Trash can	7	3	7	2	80/81
				1	Nontypable
Ward air culture	29	1	28	1	Va4/42E/52/53

plates were exposed for 30 minutes at different levels. Colonies were counted on these plates, and the average counts from 10 different operating rooms are summarized (table 6). The number of colonies of various pathogenic and nonpathogenic organisms taken from the floor is considerably greater than the number taken from the patient level. Few organisms come through the air intake. During this study, only one colony of *S. aureus* phage type 80/81 was found. The number of organisms present at 9:00 a.m. when an operation was in progress was considerably greater than when the room was clean from the previous night's washing at 8:00 a.m., or at 2:00 a.m. With the increased number of organisms at the floor level and the increase in number of colonies during operation, it would appear that many of the organisms are brought into the operating room suite on shoes and that they are stirred up from the floor by the movement of personnel. In spite of the several colonies of bacteria found, there were only nine colonies of pathogenic staphylococci. If the general precautions for maintaining cleanliness in an operating suite are maintained, the bacterial count is low in the operating room; consequently, this area is not actually an important source of postoperative infection.

TABLE 6  
*Air cultures in operating room\**

Time	Day No.	Location of Plates	Colonies per Plate
9:00 a.m. (operation in progress)	1	Floor	59
		Patient level	31
	2	Floor	26
		Patient level	43
8:00 p.m. (no operation)	2	Air intake	25
		Floor	2
		Patient level	1.5
		Air intake	2
2:00 a.m. (no operation)	2	Floor	Not done
		Patient level	2
		Air intake	1

\* Plates exposed for 30 minutes; average from 10 rooms.

Phage types†	No.	Resistant to
80/81	1	Penicillin, tetracycline, dihydrostreptomycin, chloramphenicol, erythromycin
44A	1	Penicillin, tetracycline, dihydrostreptomycin, chloramphenicol, erythromycin
44A	1	Nonresistant
Nontypable	2	Nonresistant
Va4/6/42E/77	1	Penicillin, tetracycline, dihydrostreptomycin, chloramphenicol, erythromycin
7	1	Nonresistant
7/77	1	Nonresistant
29/44A/52A	1	Nonresistant

† Phage types of the 9 colonies of staphylococci found in the operating room studies.

#### DISCUSSION OF ENVIRONMENTAL STUDIES

The above studies indicate that many staphylococci, particularly the more resistant forms, reside in the hospital. The data previously presented come from a new hospital with an outstanding housekeeping organization. Great emphasis is placed upon maintaining general cleanliness throughout the hospital. The results of the studies are similar to surveys in other university hospitals.

Bass<sup>3</sup> pointed out the prevalence of staphylococci, particularly the epidemic type 80/81, in various areas at the John Sealy Hospital, Galveston, Texas. He found that personnel in the hospital associated with patients had about a 50 per cent nose and throat carrier rate of *S. aureus* and that an appreciable number carried the 80/81 type. In contrast, freshman medical students and clerical personnel, not associated

with patients, had a 37 to 41 per cent carrier rate of staphylococci, but none carried the 80/81 strain.

There is nothing new in saying that hospitals are permanent reservoirs of infection. About 100 years ago, almost every wound became infected with pyogenic organisms or those of gas gangrene or tetanus. The larger the hospital, the more prevalent such infections. Since the advent of aseptic techniques and antibiotics, sepsis contributes only a small fraction of hospital mortality. Today any form of hospital sepsis is regarded as an avoidable complication after surgery and a slur on technique.

Hospitals appear to be the home of many truly virulent staphylococci. The more severe a lesion, the more likely it is that a patient will go to the hospital for treatment. Once the strain is introduced into this environment, it may para-



sitize new hosts and infect fresh wounds. Hospital infection represents a hazard to life. It is the duty of the staff to make the hospital safe for the patient by minimizing by adequate control measures the risk of infection.

#### MANAGEMENT OF THE STAPHYLOCOCCAL PROBLEM

There are two phases to the management of the staphylococcal problem: (1) maintenance of an environment within the hospital that prevents the harboring and spread of bacteria, and (2) treatment of the infection after it is established.

**Hospital control policies.** To make the hospital safer for the patient, it is imperative that certain control policies be set forth. Probably the most important in this area is the appointment of an infection committee, responsible for paying strict attention to all facets of the prevention of infection. The committee should maintain constant bacteriologic control studies of various areas within the hospital. Cultures should be taken in the operating room at least once a month and in the wards about every 2 months. There should be a reporting system to a central agency so that all infections are reported and careful data kept for use of the committee. Above all, a constant record of the postoperative infection rate must be maintained.

The committee should advise the hospital staff and administration concerning general control policies. These should include the continuous use of masks and strict aseptic wound care in the wards carried out with a "no touch technique," either by the use of gloves or instruments. All patients with serious staphylococcal disease should be placed in isolation. Should there be an epidemic within the hospital, the infection committee should take the lead in prescribing rigid precautions and tracing the source of the infection.

The significant carrier is the individual who has an active staphylococcal infection on the skin, in the form of either a furuncle, a sty or a small abscess. There is abundant evidence to show that staphylococcal infections on the skin can be spread to patients.<sup>4</sup> On the basis of this evidence, all personnel having staphylococcal skin infections should report to a member of the infection committee. They may have to change their place of work or take a vacation from the hospital for a short period. The most dangerous

individual is the person who is working in the ward and has a small furuncle in a covered area. Since he does not want to be discharged from work, he does not report the skin infection. This situation is dangerous because this individual is a reservoir for staphylococci and may spread the infection (fig. 1).

Every effort should be made to improve aseptic technique. A new polyvinyl film has been developed for use in the operating room.<sup>2</sup> This film adheres to the skin and serves as an excellent drape for the operative field. It is definitely an improvement in technique for many surgical operations (fig. 2).

Some method should be devised to prevent the influx of the many bacteria that come into the operating room on the shoes of the personnel. Special boots have been designed that can be placed over the shoes (fig. 3). These are conductive boots and may be sterilized by autoclaving. Such a covering for the shoes of all personnel going into the operating room is



FIG. 1. Photograph of practical nurse with small covered furuncle near axilla. This is a dangerous individual in the hospital unless her conscience dictates that she must report this infection. Skin infections are prone to disseminate staphylococci throughout the hospital environment. It is not an obvious infection and, unless she reports it, she may be responsible for the development of infection, particularly in critical areas.



FIG. 2. Application of a polyvinyl film to the skin of the chest wall before final draping and incision. This film covers the skin and eliminates the use of skin towels because an incision can be made through it. This is another improvement in aseptic technique for the operating room.

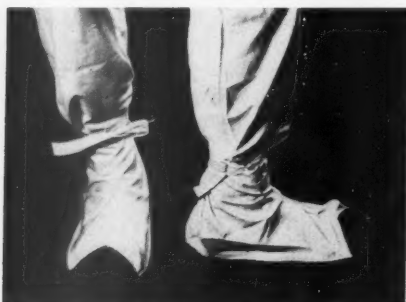


FIG. 3. Canvas boots with conductive soles for use by operating room personnel. These boots may be sterilized by autoclaving. Since shoes are a frequent source of bringing large numbers of organisms to the operating room, the use of these boots eliminates many bacteria that may be circulated through the operating room air from the floor.

another means of minimizing the number of bacteria in the air at the time of operation.<sup>1</sup>

**Susceptible patients.** The seriousness of the staphylococcal problem has increased because of the large number of susceptible patients being admitted to the hospital. It can be expected that some patients have a diminished resistance to infection. This lowered host resistance makes for an increase in sepsis. The following types of patients are particularly susceptible to infection, and every effort should be made to prevent exposure to bacteria: (1) premature and newborn infants, as well as the very aged, (2) uncontrolled diabetic patients, (3) patients receiving steroids, (4) patients who have had a recent severe viral infection, (5) severely injured or severely burned patients, (6) patients whose bacterial flora have

been altered with antibiotics, and (7) patients with leukemia and agammaglobulinemia. In some instances it might be necessary to take a culture from the nose and throat of the patient, and should staphylococci be present, temporary elimination can be achieved by the use of a local antibiotic ointment in the nose. This may prevent the patient from infecting himself if he has an open wound or surgical procedure.

**Use of antibiotics.** It is generally accepted that the overuse of prophylactic antibiotics builds up resistant forms of bacteria; consequently, part of the management of the staphylococcal problem is using prophylactic antibiotics only when necessary.

A number of surveys have shown that post-operative infection rates in hospitals which use prophylactic antibiotics routinely are higher than in those which do not. Large scale use of routine antibiotic therapy promotes the development of particularly resistant, so-called "hospital strains" of microorganisms.

Prophylactic antibiotic therapy seems indicated in the following conditions. (1) In contaminated wounds of violence and burns, particularly when adequate débridement cannot be accomplished. Antibiotic therapy is not justifiable for small burns or in every bruise or lacerated wound. It is indicated when initial surgery has been inadequate or delayed beyond 4 hours. It is also indicated when the patient has sustained penetrating wounds of the joints or major body cavities which extend into structures harboring resident bacterial flora. Therapy is instituted as soon as the patient is seen and is continued after operation for 5 days. (2) In patients who have pre-existing valvular heart disease and who receive injuries or require elective surgical procedures in the oral or pharyngeal cavity. Penicillin seems to be an effective agent in the prevention of subacute bacterial endocarditis under such circumstances. (3) In patients requiring emergency operative surgery, who have associated but unrelated infections such as furuncles, tonsillitis and pneumonitis. (4) In patients before elective lower gastrointestinal tract surgery. Antibiotics administered orally reduce both the number and virulence of intestinal organisms which may accidentally contaminate the operative wound. (5) In infants with congenital anomalies. (6) In patients who have received prolonged, high dosage steroid

therapy. (7) In elderly or debilitated patients with pre-existing pulmonary disease after prolonged anesthesia and operation. Antibiotics may be useful in controlling the subclinical infection as well as postoperative complications. (8) In patients who require indwelling catheters as a part of postoperative care. (9) In certain elective procedures performed through or in contaminated areas such as the gastrointestinal, respiratory or genitourinary tracts.

*Reservation of one or two antibiotics.* It is good practice in every hospital to put on reserve one or two antistaphylococcal agents and use them only for very resistant infections that will not respond to the usual antibiotic therapy. Many hospital infection committees insist that the newer, more potent antibiotic agents that are effective against the staphylococci, such as kanamycin and vancomycin, be withheld and not used except for overwhelming or resistant infections. This technique seems to be very sensible because it does not assist in the development of strains resistant to these agents. Most staphylococcal infections will respond to other antibiotics, and they should be used as first choice rather than the more potent, newer agents. Reservation of one or two antibiotics should provide some insurance against the development of totally resistant strains.

#### NASAL CARRIERS

The precise position of the nasal carrier of potentially pathogenic staphylococci in the genesis of clinical infection is debatable, and the proper management of such carriers is quite controversial. It is well known that the majority of hospital personnel may carry coagulase positive staphylococci in their nasal mucous membranes without clinical evidence of infection of any kind. At the present time, there is no evidence that these individuals are potentially dangerous as long as the organisms are limited to the nose and throat. Only when a person develops a skin infection is he in a position to transmit infection. Unfortunately, those individuals who carry pathogenic staphylococci in their noses have a greater tendency toward the development of skin infections.

In Caswell's<sup>4</sup> broad experience, healthy carriers have not played a major role in the transmission of staphylococcal infection. He believes, however, that persistent nasal carriers of potentially

pathogenic staphylococci should not be working in so-called key areas. There is little evidence, however, to show that nasal carriers working in the operating room or in the nursery have been responsible for many infections.

It is doubtful if nasal carriers should be treated unless they have recurring skin infections. Antibiotic jellies or ointments used daily in the nares will eliminate pathogenic staphylococci. There is, however, recolonization in 7 to 21 days after the course of treatment with local antibiotic ointments. In some instances, autogenous vaccines have eliminated pathogenic staphylococci from the nasal mucous membranes. The use of autogenous vaccines has not been clearly established. In some patients, vaccines seem to be of great benefit, particularly in those patients who carry organisms in their noses and throats and have recurring skin infections. In other instances, there is elimination of the bacteria from the nose and throat for only a period of 2 or 3 months after the course of vaccine and then these same areas are recolonized by the same organism. Some patients with multiple skin infections have received little or no benefit from the vaccines. At the present time, it seems that an attempt should be made with local antibiotics to remove the staphylococcal organisms from the noses of those individuals who are undergoing operative procedures or who have multiple skin infections. When recurring skin infections persist, it is worthwhile to attempt the use of a phenol or heat killed autogenous vaccine, but its therapeutic effectiveness is debatable. Martin, Nichols and Henderson<sup>6</sup> believe that it is reasonable in certain situations to attempt to control the carrier state temporarily by the use of antibiotics intranasally. They state that the question of whether the healthy carrier is a major source of danger in the genesis of clinical infections cannot be answered at this time. It is their opinion that if there is evidence that a person is disseminating a virulent strain responsible for clinical infection, removal of that individual from the hospital environment is obligatory. Obviously many medical, economic and psychologic factors must be considered in evaluating nasal carriers of staphylococci. When more than half of the hospital personnel carry coagulase positive staphylococci in their noses and throats, it is obvious that all of them cannot be eliminated.

## SUMMARY

The trend in sensitivity pattern of staphylococci isolated from patients is one of increasing resistance. During the first 5 months of 1960, of 716 cultures of *Staphylococcus aureus* from patients in the hospital 80 per cent showed resistance to penicillin, 51 per cent to chloramphenicol, and 8 per cent to novobiocin. About 58 per cent of these organisms were of the "hospital strain" 80/81 phage type. This is the truly troublesome organism in most institutions.

Fifty-three per cent of hospital personnel and 44 per cent of patients on admission were found to have coagulase positive staphylococci in their noses and throats. In a survey of the surrounding community, 37 per cent of the nose and throat cultures contained coagulase positive staphylococci. Phage type 80/81 was much more prevalent in the hospital personnel than in the community.

A study of 184 patients on the medical and surgical wards, with an average hospital stay of 9 days, showed that 12 per cent became carriers of coagulase positive staphylococci in their noses and throats.

Staphylococci do inhabit hospitals. Their control must be the constant concern of the surgeon and hospital administration. Improvement in aseptic techniques in all hospital areas is the best defense against these microorganisms. It is doubtful whether nasal carriers transmit

sepsis. Anyone with an active skin infection does spread the microorganisms and is dangerous. Every hospital should have an infection committee that pursues with vigor environmental studies and rigid control policies.

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## MAJOR COMPLICATIONS OF BILIARY TRACT SURGERY\*

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The statement that few surgical procedures yield better results than cholecystectomy is true only if certain conditions are met:

1. The gallbladder, the common bile duct, or both structures must be the real site of the disease process responsible for the patient's symptoms. No matter how closely the symptoms resemble those of a diseased gallbladder, they will not be relieved by the removal of an innocuous organ. Cholecystectomy will not alter the pathologic changes arising from an ulcer on the posterior wall of the duodenum, for instance, nor will it benefit the patient whose symptoms are due to a gastrointestinal allergy or to domestic unhappiness. The removal of the gallbladder, in fact, will do nothing more than compound those difficulties.

2. The operation must be performed competently. An incompetently performed cholecystectomy may be promptly lethal. If it is not, it may leave pathologic complications incompatible with comfort, with life or with both. Such complications require surgical correction, and the procedure often taxes the skill and judgment of the most dexterous and most experienced surgeon. The repair of damage done at biliary tract surgery is always difficult. No matter how well it is done, secondary surgery always has lethal possibilities. It may not be successful, and it may itself give rise to additional complications. In either event, further surgery is necessary. Aside from other problems, the economic loss to patients who have had the misfortune to suffer a stricture of the common bile duct is enormous. The life span of many of these patients, even if they survive repeated operations, is often sharply reduced. The progressive development of coronary sclerosis on the part of the surgeon who is called upon to repair such strictures is another of their unhappy side-effects.

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### PREVENTIVE MEASURES

Cliché though it be, a discussion of complications of gallbladder surgery must begin with the statement that their only truly satisfactory treatment lies in their prevention. Most catastrophes that occur in connection with operations on the biliary tract can be prevented if the proper safeguards are employed.

1. The surgeon must be competent. This implies both that he has a trained and competent surgical team to assist him and that he is himself thoroughly familiar with the upper abdominal quadrant and its possible anatomic variations (figs. 1 to 11).§ If he is not thus qualified, he should not undertake biliary tract surgery. The patient will pay a high penalty for his ignorance in resultant of hemorrhage, ductal strictures, biliary fistulas, overlooked stones and hepatic necrosis consequent upon the ligation of the right hepatic or the common hepatic artery.

2. The anesthesia used must provide for relaxation within the limits of safety.

3. The incision must be long enough to provide adequate exposure.

4. The surgical field must be thoroughly illuminated. A large portion of common bile duct injuries occur because an inexperienced surgeon does not know, or cannot see what he is doing.

If these considerations are met, all the surgical circumstances are favorable. It is then the surgeon's responsibility to identify positively the structures he proposes to divide. In particular, he must be certain that he divides no blood vessel in the region of the common or the cystic duct until he has traced it to its point of entrance into the gallbladder.

One or two other points must be made with regard to cholecystectomy. First, there is no merit in swiftness *per se*. An operation concluded rapidly at the expense of good surgical technique has no place in a surgical amphitheater; it belongs in the stockyard. Second, biliary tract

§ All the figures in this paper are from Cole, W. H. *Operative Technique, General Surgery*, Vol. 1, 2nd ed., Appleton-Century-Crofts, Inc., 1955.



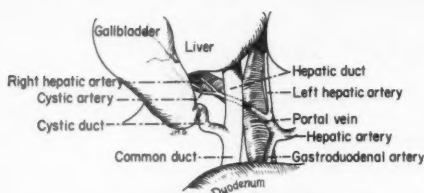


FIG. 1. Normal gallbladder and anterior portion of liver reflected upward for exposure.

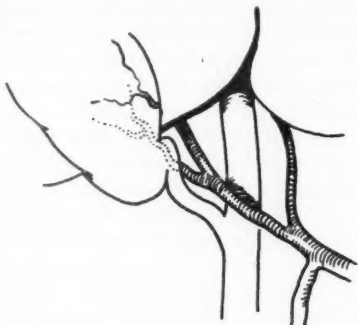


FIG. 2. Right hepatic or main hepatic artery anterior common duct; frequency, 12 per cent. *Danger:* ligation of hepatic artery for cystic, or injury to common duct.

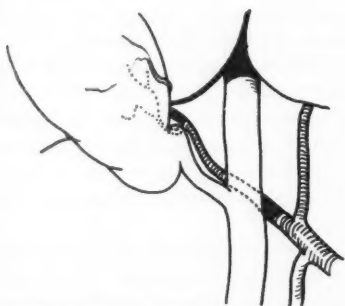


FIG. 3. Right hepatic artery lying close to cystic duct; frequency, 20 per cent. *Danger:* ligation by mistaking it for cystic artery.

surgery is physically and mentally taxing. If the surgical list is so heavy that a secondary operation on the duct cannot be booked early in the day, it should be booked on another day, or a surgeon with a less heavy service should undertake it. Similarly, the surgeon should be free from the pressure of having to get to his office on time to see patients or to fulfill some other engagement. This is the type of surgery that demands all that a surgeon has to give in the way of dedication as well as competence.

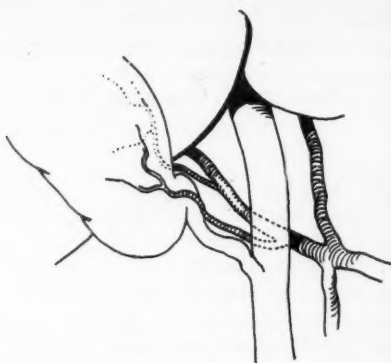


FIG. 4. Two cystic arteries; frequency, 15 per cent. *Danger:* after ligation of one, the second may be cut and common duct injured while controlling bleeding.

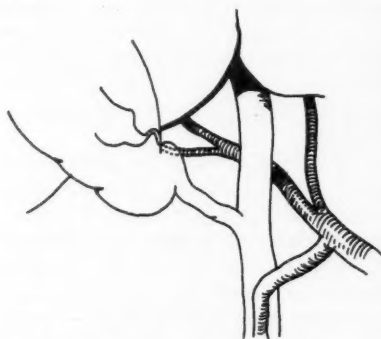


FIG. 5. Gastroduodenal artery anterior to common duct; frequency, 10 per cent. *Danger:* injury to artery or to common duct.

*Technical precautions.* Certain practices at operation help to prevent injuries of the common and hepatic bile ducts.

1. Tenting of the common duct at the time the cystic duct is clamped and divided is undesirable and should be avoided. The application of a clamp to the duct while the gallbladder is held in firm traction, although the clamp is intended to include only the cystic duct, may well enough damage the common or right hepatic duct, with disastrous consequences.

2. Inflexible insistence upon division of the cystic duct at the precise point at which it enters the common duct is both unnecessary and unwise. For years the senior author has followed the practice of leaving *in situ* a few millimeters of cystic duct, with due care to see that there is no stone left in the stump, and has never encountered any postoperative difficulty as a result. On the

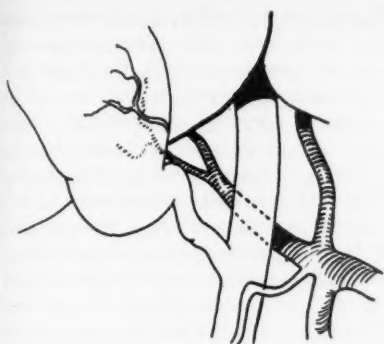


FIG. 6. Branch of hepatic or gastroduodenal artery in anterior wall of common duct; frequency, 30 to 50 per cent. Usually cut, but bleeding never serious.

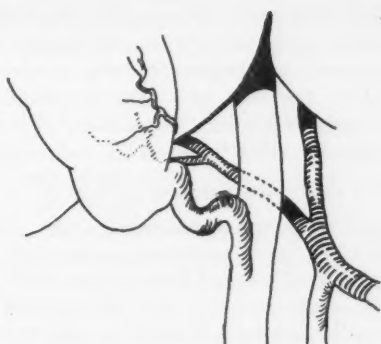


FIG. 9. Cystic duct lies parallel to or spirals around common duct; frequency, 23 per cent. *Danger:* injury to common duct while removing cystic duct.

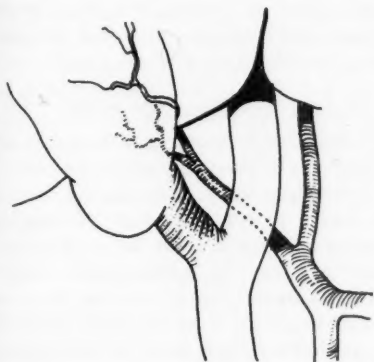


FIG. 7. Very short but large cystic duct. *Danger:* trauma to, or ligation of common duct while ligating cystic duct.

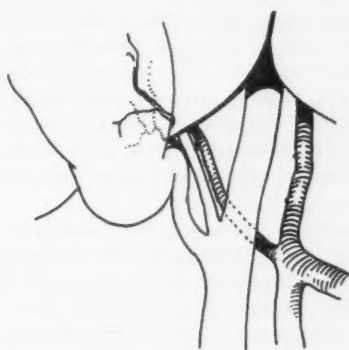


FIG. 10. Accessory hepatic duct may empty into hepatic duct or gallbladder, frequency, 15 per cent. *Danger:* if accessory duct is cut and not ligated, bile peritonitis or abscess may result.



FIG. 8. Mobile common duct. *Danger:* extreme mobility may cause careless surgeon to clamp and cut it with cystic duct.

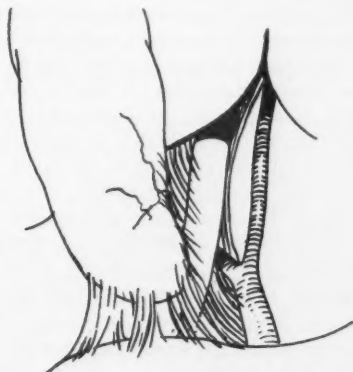


FIG. 11. Large pendulous Hartmann's pouch. *Danger:* injury or actual excision of part of common duct during removal of gallbladder.

contrary, on a number of occasions we have done secondary operations for severe strictures of the common duct because the surgeons who did the first operation had unwisely attempted total extirpation of the cystic duct and thus had damaged the common duct.

#### HEMORRHAGE DURING OPERATION

The complication of gallbladder surgery which carries the most immediate consequences is hemorrhage. There are few areas in which the blood supply casually described as "normal" in texts of anatomy and surgery has more variants than the area of the liver and biliary tract. Some of the variants are observed frequently and some infrequently, but not more than 50 per cent of all cases fall into the so-called normal group (figs. 1 through 6).

The surgeon who refrains from using his scalpel until he visualizes the entire area and identifies each structure will seldom come to grief from hemorrhage or any other complication. Failure to identify the cystic, common and hepatic ducts and the cystic, right hepatic and common hepatic arteries is an invitation to disaster.

When the cystic artery, for one reason or another, eludes the surgeon, what happens next depends upon his experience and his ability to maintain his poise in an emergency. Hemorrhage from the cystic artery is not immediately fatal, but unwise handling may produce a fatality. The simplest way to deal with it is to insert the index finger in the foramen of Winslow and compress the hepatic artery between the finger and the thumb. The blood which has filled the surgical field can then be removed by suction and the severed cystic artery, under full vision, can be identified and can be secured by ligature.

This is not the procedure of the inexperienced surgeon. Unaccustomed to emergencies, unable to deal with the hemorrhage in a composed and intelligent fashion, he is likely to panic. Confronted with what appears to be a devastating hemorrhage, he seeks to control it by the blind application of the largest hemostat or hemostats on the instrument tray. Conceivably, a hemostat applied deep in a pool of blood might catch only the bleeding cystic artery, but the chances are against it. It is much more likely that the main branch of the hepatic artery, the right hepatic artery, the common or hepatic duct, or some other vital structure will be grasped.

Thus a procedure which, under correct management, might have been performed easily, instantly becomes fraught with deadly peril. Then the inexperienced surgeon is likely to compound his original error by applying the heaviest chromic catgut ligature available and closing the wound without further manipulations.

A prompt fatality is not unusual. If it does not occur, the chances are that complications will develop, perhaps almost immediately, and will require immediate management. If they are deferred, it is a rather general practice for the patient to be referred to another surgeon, usually at a fairly distant point, with the assurance that the trouble is really not too serious but the surgeon who conducted the original surgical orgy does not, for one reason or another, wish to undertake the secondary operation. This may be interpreted as meaning that he is stepping out from under the consequences of his original surgical ineptitude.

#### STRICTURES OF THE COMMON BILE DUCT

The majority of strictures of the common bile duct are due to direct surgical trauma, but they are occasionally due to other causes.

1. Failure to establish proper drainage after cholecystectomy may result in puddling of bile about the ducts, with subsequent cholangitis.
2. Postoperative leakage of bile may occur from other sources than the cystic duct. After the gallbladder has been removed, careful search should be made for possible accessory ducts in the raw hepatic space. If they are found, ligatures should be placed about them.
3. Strictures of inflammatory origin may appear some months after operation.
4. Chronic diffuse sclerosing pancreatitis is another possible cause of common bile duct strictures.

All these strictures are unusual, and all of them, like strictures of traumatic origin, must be treated surgically.

*Timing of surgical repair.* If damage to the common bile duct is recognized when it occurs at operation, that is the optimal time for repair. End-to-end, mucosa-to-mucosa, tension-free anastomosis of the duct over the limb of a T-tube will usually give excellent results. The T-tube must not emerge at the point of anastomosis. Our personal experience with surgical injury of the common bile duct is limited to a single patient. The unfortunate accident was, for-

fortunately, recognized as soon as it occurred, and repair was undertaken by this technique. The patient made a good recovery, lived to a considerable age, never had symptoms referable to the liver or bile ducts, and died of causes not connected with the hepatobiliary tract.

In most injuries of the common duct, repair is necessarily deferred because they are inflicted by surgeons of relative or absolute inexperience, who are unlikely to recognize them.

If the damage is recognized soon after operation, that is, within 8 to 10 days, the patient's best interests are served by immediate repair by the technique just described. Operation is much simpler at this time than later; bleeding is not likely to be profuse, adhesions will not be troublesome, and a satisfactory result may be anticipated.

If, as usually happens, the damage is not repaired at operation or repair is not undertaken in the immediate postoperative period, it is best to defer reparative surgery for 6 or 8 weeks. It should then be undertaken only by an experienced surgeon, who, in the light of his past experience, will need no warning as to technical and other difficulties which lie ahead of him.

*Technique of deferred repair.* The technique of deferred repair of common bile duct strictures is as follows. Opening the abdomen without damage to the bowel inevitably involved in the pathologic process is the first hazard, and it is a genuine one. The incision must be adequate. Personally, we prefer a long, vertical rectus incision extending from the xiphoid process to well below the umbilicus. Whatever type of incision is used, every effort should be made to enter the abdomen at a point likely to be relatively free from adhesions, which generally means well down on the abdomen.

The next task is the methodical disentanglement of the anatomically distorted structures, in which the usual planes of cleavage no longer exist. The multiple blood vessels present in these tissues are a source of steady blood loss, for which due compensation must be made.

After a generous incision and separation of the omentum and viscera from the peritoneum, the hepatic flexure of the colon and the proximal portion of the transverse colon are turned downward and to the left. The undersurface of the liver is now exposed; this is a very delicate and difficult part of the operation. An incision is made lateral to the duodenum, which is

rotated mesially, thus exposing the vena cava, the aorta, the head of the pancreas, the lower end of the stomach and the pylorus. The ovarian or spermatic vessels are also visualized. In the course of the dissection, the hepatic artery must be identified and protected against damage, and the mass of adhesions about the liver must be freed with the greatest caution.

The purpose of the dissection just described is the identification of the proximal and distal ends of the damaged common duct. Ultimately, as the dissection continues down the liver, one reaches the large lymph node described by Cattell as lying on the postero inferior aspect of the gastrohepatic ligament and serving as a highly accurate guide to the duct. When the duct is presumably reached, it is always well to aspirate it, to be certain that the structure is the duct. If blood and not bile is secured, then the attempt at identification must be begun again.

One reason for the demonstration and utilization of the distal end of the common duct, whenever this can be achieved, is that it is then possible to preserve the valuable sphincter of Oddi, a structure which it is beyond the power of the surgeon to duplicate. If, however, the distal end of the duct cannot be found by a careful search, the proximal end must positively be found, no matter how much time and patience are required, and even if the substance of the liver must be entered. The patient is not likely to benefit by the creation of a biliary fistula, with later transplantation of the fistula into the duodenum, or by simple anastomosis of part of the small bowel to the undersurface of the liver. There is no reasonable hope of a successful end result, in fact, unless the duct, not the liver, is anastomosed to some portion of the intestinal tract.

If the proximal and distal ends of the common duct are found and are suitable for end-to-end anastomosis, that, as already pointed out, is the procedure of choice. It is important that the T-tube shall not emerge at the site of the anastomosis; if this technique is used, the anastomosis is likely to break down. The best plan is to make a separate incision well below the point of anastomosis, with one end of the tube passing upward toward the hepatic ducts beyond the site of the anastomosis; the distal end passes downward toward the duodenum. The tube

should be allowed to remain in place for a fairly long time, perhaps a minimum of 6 months.

If the proximal and distal ends of the common duct are not suitable for anastomosis, and in our experience they usually are not, the best results are accomplished by anticolic anastomosis of the jejunum to the proximal end of the common duct by the Roux-en-Y technique, with enteroanastomosis below the hepaticojejunostomy, as advocated by Cole and the late Arther W. Allen. After the anastomosis is completed, one must make certain that hemostasis is satisfactory. The raw area should be peritonealized as far as possible and a Penrose drain placed down to the point of anastomosis before the abdomen is closed. In our experience, cholangitis or hepatitis is less frequent after this type of repair than after the simpler procedure of anastomosing the duct to the duodenum.

#### OVERLOOKED STONES

Most surgeons would agree that the common bile duct should be explored if it is enlarged, if a stone or stones can be palpated in it, if the patient is or has been jaundiced, and if there are multiple small stones in the gallbladder and the cystic duct is enlarged. In the experience of the senior author, the common duct has been explored in about 25 per cent of all patients subjected to cholecystectomy and one or more stones have been found in about half of the ducts explored. If the duct is not enlarged, however, or is really small, we require positive indications to explore it. In our experience, exploration of a small duct is technically difficult and is usually not fruitful.

After the duct has been opened, a careful search is made for stones. Scoops are passed into it and into each of the hepatic ducts. After all stones have been removed, or if no stones are found, progressively larger Bakes dilators, up to 7 to 8 mm., are passed through the sphincter into the duodenum. One must be certain that the dilator has passed into the duodenum, even an experienced surgeon may be misled on this point, and that there is no obstruction at the ampulla. If an obstruction exists at this point and is not relieved, the patient's symptoms are not likely to be relieved either.

Obstruction at the ampulla may result from several causes, including ascending infection from the duodenum; an impacted stone, particularly

if the impaction has been of long duration; a new growth; fibrosis from a previous pancreatitis; or too vigorous instrumentation when the common duct was explored at a previous operation. If there is no obstruction, the sphincter can usually be dilated gradually. Forceful passage of probes or dilators is dangerous and should never be practiced.

After dilatation has been completed, the common duct is thoroughly lavaged with physiologic salt solution, which is removed with fairly strong suction. Additional stones or sand will occasionally be removed with the fluid.

A catheter is now passed through the duct into the duodenum and additional lavage is performed. If there is no leakage from the opening into the common duct and if the duodenum is observed to distend as the solution is introduced, then it may be safely assumed that there is no obstruction at the ampulla.

It is sometimes impossible to pass dilators through the ampulla even when there is no evident obstruction from stones, fibrosis or other causes. In such cases, the best plan is to open the duodenum by a short incision directly over the ampulla, the exact position of which has been identified by passing a Bakes dilator down to it. It can thus be determined, by direct inspection, what the cause of the difficulty is. An impacted stone can be removed, or, if necessary, a sphincterotomy can be performed. Our experience with this procedure, although limited, has been very satisfactory. If the sphincter must be divided, the incision should be made at 11 o'clock. Sutures are seldom necessary to control bleeding; if they are used, they must be placed with great care.

We have had no experience, nor do we expect to have any experience, with the so-called blind sphincterotomy. It is another open invitation to disaster. On the other hand, transduodenal exploration of the ampulla is not free from risk and should be reserved for cases in which the desired results cannot be achieved by simpler means.

After the ampullary procedure has been completed, a T-tube is inserted into the common duct and a watertight closure about it is accomplished with fine chromic catgut. If the distal end of the T-tube has been passed into the duodenum, one must be certain that the tube is definitely smaller than the lumen of the



duct. The tube must be sufficiently small to cause no pressure on the ampulla, which might cause necrosis, and not to obstruct the pancreatic duct. With these precautions, this is a very satisfactory technique.

**Cholangiography.** Surgeons whose opinions we greatly respect think highly of cholangiography at operation, to make sure that all stones have been removed from the biliary tract. In our own limited experience with it, perhaps because our experience with it is so limited, we have found it more productive of confusion than of information. We cannot say that the measures we have just outlined are unfailingly satisfactory, but we think we can fairly say that with them we have overlooked as few stones as have surgeons who use operative cholangiography.

Cholangiography is a very valuable post-operative measure, to determine the status of bile ducts before the common duct tube is removed, usually about the 10th day. If the opaque medium enters the duodenum freely, it is usually safe to remove the tube.

**Management of overlooked stones.** It is entirely possible that small stones are overlooked at operation rather frequently. It is also possible, in spite of all precautions, including cholangiography at operation, that larger stones are occasionally overlooked. If there is no obstruction at the ampulla, a small stone or stones will often pass spontaneously. Furthermore, the prolonged ductal drainage and the change in the quality of the bile after cholecystectomy encourage the dissolution of small stones and their spontaneous passage.

If, however, obstruction does occur from a stone that does not pass spontaneously, re-exploration of the bile duct will be necessary for its removal. On the other hand, the operation is not urgent and should not be undertaken hastily.

#### PROBLEMS OF ACUTE CHOLECYSTITIS

Acute cholecystitis is by no means uncommon, nor is complicating gangrene of the gallbladder. From 1945 through 1958, 118 of 1431 gallbladders examined in our Department of Pathology were acutely inflamed.

A large number of patients with acute disease will have stones in the gallbladder. Most of them will have an impacted stone in the cystic duct, and a moderate number will have stones in the common duct.

How a patient with acute cholecystitis should be treated depends upon when the patient is seen:

1. A patient who has been referred promptly presents no major problems. If the surgeon to whom he is referred is an advocate of immediate surgery for acute cholecystitis (and the senior author is), he can perform the cholecystectomy and explore the common duct with little increased difficulty.

2. A patient who is not seen until after he has been ill for several days presents a somewhat different, and considerably more difficult, problem. If he improves promptly under conservative measures, including replacement therapy to maintain the correct fluid balance and adequate antibiotic therapy, exploration can safely and desirably be deferred for 6 to 8 weeks.

3. If the patient's progress under conservative measures is not satisfactory, he must be prepared for operation as rapidly as possible, even though exploration is performed with a known increase in risk. Any surgical procedure at this stage is difficult and often dangerous. The anatomical landmarks are likely to be obscured. Inflamed tissues are difficult to handle. Without the exercise of extreme care, exsanguinating hemorrhage may be caused by injury to the blood supply, or injury of one of the other vital structures is possible.

There are several courses open to the surgeon:

1. If it seems safe, he can perform definitive surgery by exposing the common duct just at the supraduodenal portion, opening it, and passing a Bakes dilator up the common duct to the hepatic duct. With the common duct thus positively identified, cholecystectomy can safely be proceeded with. This is a desirable, but not always a possible, procedure in acute cholecystitis.

2. If the surgeon feels uncertain of his ability to perform definitive surgery in the circumstances, or if it proves impossible to identify beyond doubt all the important structures, then cholecystostomy should be resorted to. Stones in the gallbladder should be removed, and an impacted stone or stones in the cystic duct should also be removed. The surgeon should feel no embarrassment in resorting to this procedure and should make no apologies for his course. Cholecystostomy is not often indicated. It is seldom curative. But it is sometimes lifesaving,

and there should be no hesitancy in resorting to it when it seems to be.

3. Partial cholecystectomy, as was suggested many years ago, is also a possibility. The portion of the gallbladder not attached to the liver is cut away; the stones are removed; the mucosa is destroyed chemically by carbolic acid and alcohol or some chemical agent; a tube is placed over the area of destroyed mucosa; and the margins of the remaining portion of the gallbladder, denuded of mucosa, are sutured together. The tube is brought out through a separate lateral stab wound.

#### BILIARY PERITONITIS

Postoperative hemorrhage is the only immediate complication likely to be confused with biliary peritonitis. The patient who becomes abnormally restless fairly soon after cholecystectomy, whose pulse rate increases, who complains of severe pain, and who goes into acute shock may be bleeding from a slipped ligature. That diagnosis should always be considered. If, however, appropriate drainage was not established, or if it was established and the dressings are found soaked with bile, then it must be assumed that significant bile leakage is occurring and biliary peritonitis, almost always of chemical origin, is the more likely diagnosis. We have

never seen bile peritonitis in a patient who had proper drainage at cholecystectomy.

Whether the condition is postoperative bleeding or biliary peritonitis, immediate re-opening of the wound is necessary. If biliary peritonitis is present, the bile in the peritoneal cavity is removed by suction and proper drainage is established. A calm appraisal of the situation, with evacuation of the bile and provision for drainage, will save the patient from the fatality likely to ensue if dilatory tactics are followed for any considerable time.

#### SUMMARY

Cholecystectomy is an extremely satisfactory surgical procedure if the patient's symptoms really arise from a diseased gallbladder and if the operation is performed competently. Otherwise, it may give rise to complications that require difficult and dangerous surgery. The commonest of these are hemorrhage at operation, strictures of the common bile duct, overlooked stones, biliary peritonitis, and the various complications associated with surgery during acute or gangrenous cholecystitis. The best way to handle these complications is not to let them occur; most of them are readily preventable. Principles and techniques of correction are described.

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## REGIONAL PERFUSION OF TUMORS USING THE PUMP OXYGENATOR\*

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For some time it has been apparent that surgery and external radiation have been extended almost to the limits of feasibility in the management of tumors. Yet the results of therapy have been poor in a vast number of instances. Therefore, the search for truly effective and reasonably safe anticancer drugs has been tremendously accelerated, and agents have been found which will destroy neoplastic tissue. Unfortunately, most of these chemicals are also detrimental to normal body cells, and many of them are particularly damaging to the vital blood forming cells of the bone marrow.

In an effort to deliver a maximal dose of anti-tumor agent to the region affected by the neoplasm while achieving minimal dosage to the rest of the body, Klopp and his associates<sup>1</sup> examined the technique of intra-arterial administration of the nitrogen mustard compounds. Subsequently Creech and his co-workers<sup>2, 5</sup> extended this concept by employing the pump oxygenator to provide a period of continuous perfusion of the agent through the artery to the part involved, while in large measure excluding the rest of the vascular system by means of appropriately placed tourniquets.

The purpose of the present paper is to report certain of our experiences with this method of cancer chemotherapy. It should be stated at the outset that currently we look upon regional perfusion as a form of palliation rather than cure. Surgery and/or radiation should always be used when applicable with the prospect of cure. Nevertheless, the concept of regional perfusion is a sound one. It is being explored not only to provide palliation when possible, but also to provide solid technical and physiologic information which will be useful as even more effective anticancer drugs are developed.

### METHOD

At the present time two teams working simultaneously are used. One team, composed of the surgeon and his assistants, performs the surgical portion of the procedure; the other team, consisting of a physician and a technician familiar with the extracorporeal circuit, assembles and operates the perfusion apparatus (fig. 1). In our clinic, the extracorporeal circuit used consists of a Sigmamotor pump and a disposable bubble oxygenator which has a reservoir capacity of 500 ml. The oxygenator is primed with 500 ml. of fresh heparinized blood drawn from the patient just before surgery and replaced with 500 ml. of citrated bank blood. The artery and vein to be employed are exposed surgically and, after proximal occlusion, are cannulated with polyethylene catheters. The patient is then heparinized with 2 mg. per kg. of heparin administered intravenously by the anesthesiologist. To insure total occlusion, a tourniquet is placed around the part proximally. The pump is started and, after adequate flow has been obtained, the chemotherapeutic agent is administered into the circuit behind the arterial head of the pump. This may be injected either in multiple increments or in a constant drip. The character of the agent determines how long the pump is to run after completion of injection. The blood is oxygenated with 100 per cent oxygen at 3 to 5 L. per minute. The rate of flow of the pump is determined by the anatomic part being perfused. In the extremities, we employ a rather low flow rate of 150 to 200 ml. per minute to insure adequate venous return. After completion of the perfusion, the part may or may not be flushed out depending on the agent used. The pump is stopped, the tourniquet removed, and the cannulas are taken out of the vessels. Usually the incisions in the vessels are sutured with cardiovascular silk sutures. Protamine sulfate in divided doses is administered intravenously by the anesthesiologist in the dose of 1 mg. per

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FIG. 1. Equipment employed in regional perfusion: Sigmamotor pump, disposal bubble oxygenator and oxygen supply.

each mg. of heparin. This procedure may be used as an adjunct to surgical excision of the lesion and the lymph drainage area involved, or as a primary form of therapy.

#### *Head and Neck Tumors*

**External carotid.** For inoperable lesions of the oropharynx, the external carotid artery and the internal and external jugular veins are used (fig. 2). They are exposed through a longitudinal incision, and the external carotid is cannulated immediately cephalad to the superior thyroid artery. Cannulas are placed in both the external and the internal jugular veins and joined to a Y-connector. The flow rate varies between 100 and 150 ml. per minute. Leakage is usually very great. Several groups of investigators<sup>6,9</sup> cannulate both carotids and perfuse both sides simultaneously because of the cross anastomosis of vessels. Only time will tell which procedure is the better one. A tourniquet is placed just above the eyebrows to prevent excessive leakage and flow to the scalp.

**Internal carotid perfusion.** The internal carotid arteries and the internal jugular vein bilaterally have been used in the case of inoperable lesions

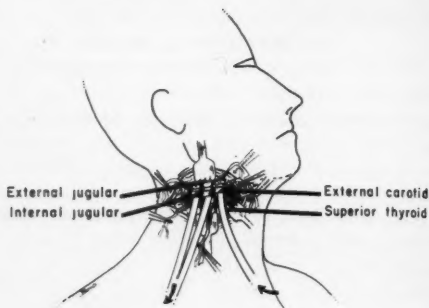


FIG. 2. Lower extremity perfusion using the femoral artery and vein.

of the brain and the scalp in a manner similar to the external carotid artery perfusion.

#### *Tumors of the Upper Extremity*

For lesions involving the hand and forearm, the brachial artery and vein are used. If the tumor involves the upper arm or if spread has occurred to the axilla, then the axillary artery and vein are used (fig. 3). Isolation is fairly complete when a tourniquet is placed through the axilla and over the shoulder. This procedure is followed by axillary node dissection.

#### *Pelvic Tumors*

Perfusion may also be utilized for inoperable or recurrent lesions of the pelvis (fig. 4). The aorta and vena cava are approached through a midline abdominal incision. The lumbar vessels are divided, and the aorta and vena cava are mobilized; umbilical tapes are placed around them, and they are cannulated with large catheters distally. If periaortic nodes make exposure of the vessel difficult, then the aorta and vena cava are cannulated indirectly through the femoral artery and vein. The inferior mesenteric artery and vein, superior hemorrhoidal vein, posterior hypogastric artery, external iliac vessels and testicular vessels are temporarily occluded. Tourniquets are placed around both lower extremities, and perfusion is begun at a flow rate of 150 to 200 ml. per minute.

#### *Tumors of the Lower Extremity*

**Iliac perfusion.** This procedure is used for lesions which are too high for femoral vessel perfusion. The iliac vessels are approached through a low oblique abdominal incision,

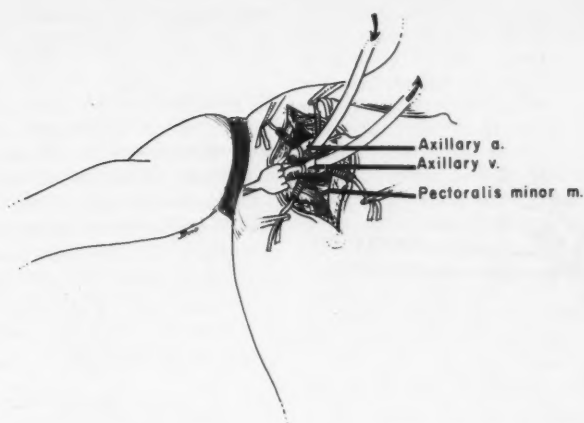


FIG. 3. Upper extremity perfusion using the axillary artery and vein

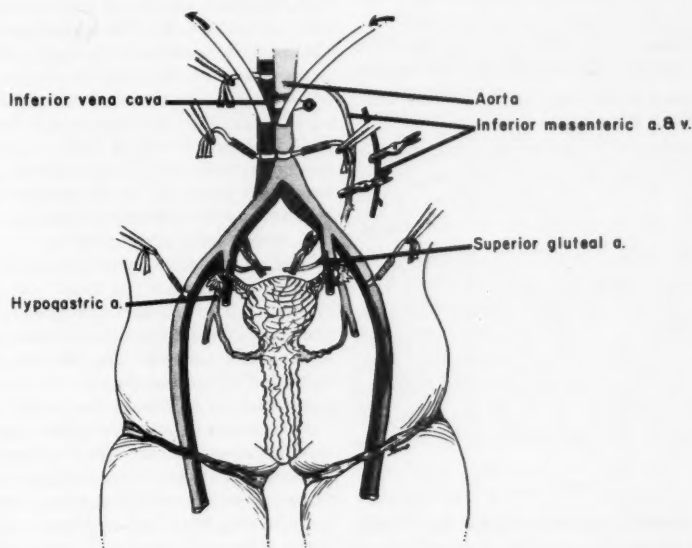


FIG. 4. Oropharyngeal perfusion using the external carotid artery and the internal and external jugular veins.

the peritonium and contents being reflected medially. Usually a preliminary extensive lymph node dissection is performed from the bifurcation of the external and internal iliac down to the inguinal ligament. Also the inferior epigastric, deep circumflex iliac and the obturator vessels are ligated in order to reduce leakage systematically. The external iliac artery and vein are then cannulated, the tips of the catheters ex-

tending down to the femoral vessels. The tourniquet is applied as for femoral perfusion. The flow rate varies from 150 to 200 ml. per minute.

*Femoral perfusion.* This technique is used for lesions above the knee and below the inguinal ligament. If lymph nodes are present we excise these through a longitudinal incision just below the inguinal ligament. The femoral artery and vein are cannulated between tapes, and a tourni-



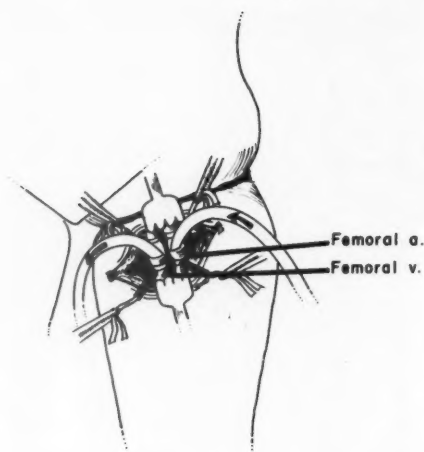


FIG. 5. Pelvic perfusion

quet is tightened above this area (fig. 5). The tourniquet is held in place by means of a Steinmann pin placed in the iliac crest. The flow rate is usually 200 to 400 ml. per minute.

**Popliteal perfusion.** This procedure is employed for lesion on the foot and below the knee. It has the advantage of only minimal leakage of the drug because of the ability to isolate almost completely the part from the rest of the body. The thigh is flexed, and the popliteal artery and vein exposed through a longitudinal incision on the medial aspect of the thigh just above the popliteal area. Tapes are placed above and below the vessels, and the catheter is inserted distally. A tourniquet is used in the midthigh area. The flow rate is usually from 50 to 100 ml. per minute.

#### DRUGS

Various chemotherapeutic agents are being tried in an attempt to determine a specific drug for a specific group of tumors. The agents most commonly being used are the alkylating agents, nitrogen mustard ( $\text{HN}_2$ ), phenylalanine mustard, triethylene melamine, Cytosin and triethylene-thiophosphoramide; the antimetabolites, 5-fluorouracil and aminopterin; the antibiotics, actinomycin D and streptovitamin A; and the combined alkylating antimetabolites, AB-100 and U-8344. We have also employed unsuccessfully another antimetabolite, 6-mercaptopurine riboside. The most successful agents so far have been nitrogen mustard and phenylalanine mustard.

**Side effects.** The side effects are due usually to the radiomimetic effects of the agents being used or to the surgical procedure employed. Local effects such as edema of the part or vesiculation and discoloration of the skin have occurred. We have encountered no difficulties with clotting in either the arterial or the venous system. When Cytosin has been used, we have encountered local alopecia, but no alopecia totalis. The use of nitrogen mustard has caused a drop in the total white blood cell and platelet count, but this was only temporary. Gastrointestinal symptoms have been mild, with only occasional nausea being reported.

#### CASE REPORTS

##### Head-Neck Perfusion

**Case 1.** This 69-year-old colored woman had had two previous excisions of a lesion situated in the floor of the mouth. The pathologic report was "anaplastic carcinoma, probably mucous adenocarcinoma of the floor of the mouth." When she was referred to the University Medical Center on February 20, 1960, there was a fungoid growth in the floor of the mouth on the right and a large mass of lymph nodes in the submandibular area. Since this lesion was nonresectable and because this tumor was very susceptible to an antimetabolite, 6-mercaptopurine riboside, it was decided to perfuse the oropharynx. On April 5, 1960, under general anesthesia, the right oropharynx was perfused with 4 gm. of 6-mercaptopurine riboside, utilizing the right external carotid artery and the internal jugular vein. The patient did well post-operatively, with no drop in the white blood cell count and no change in the platelet count. The lesion, however, did not respond to the agent used and there was no regression in its size. 6-Mercaptopurine riboside is usually effective against abnormal mucus-producing tissue, but the therapy must be long term and continued over a period of several weeks systemically before any response can be noted.

##### Arm Perfusion

**Case 2.** This 78-year-old white woman several months before being referred to us had undergone a wide excision of a black lesion of the right arm in the brachial area and a radical axillary dissection. The pathologist reported "malignant melanoma" with one positive node low in the axilla. She was later referred to the University Medical Center with local recurrence. On August 20, 1959, with the use of the brachial artery and vein, the right arm was perfused with 105 mg. of phenyl-

alanine mustard and 56 mg. of triethylenethiophosphoramide; a supraclavicular node was removed for biopsy purposes. The postoperative course was characterized by pain in the arm, edema, brownish discoloration and some vesicle formation. The mass regressed in size by several inches. The white blood cell count dropped from 5920 preoperatively to 3050 on the 7th postoperative day, but gradually rose thereafter. The platelet count did not vary. On September 2, 1959, the 13th day after perfusion, the lesion of the arm was widely excised surgically and a skin graft applied. The patient responded well to this procedure.

#### *Pelvic Perfusion*

*Case 3.* A 35-year-old colored woman was first seen at the University Medical Center in January, 1959, where a biopsy of a cervical lesion revealed "anaplastic spindle cell malignancy of the cervix." A radical hysterectomy with a combined vaginal and abdominal approach was performed on January 25, 1959. After this procedure, the patient received radiation to the pelvis and the abdomen. On June 16, 1960, she was examined, and a 5-by 6-cm lesion was found on the left lateral aspect of the pelvic wall. Because the patient had already had radical surgery and cobalt therapy, perfusion was considered the treatment of choice. Consequently, on June 22, 1960, she was taken to surgery and, under general anesthesia, a perfusion of the pelvis was performed in which 2800 hundred mg. of Cytoxan were utilized. This procedure was performed through an abdominal incision, catheters being placed in both common iliac arteries and the inferior vena cava. The external iliac arteries and the posterior divisions of the hypogastric and hemorrhoidal veins were temporarily clamped. Postoperatively, the patient exhibited a fall in the platelet count on the 1st day from 220,000 preoperatively to 90,000, but the count gradually rose until the 14th postoperative day, when it was again 200,000. The white count decreased after a temporary increase, but never went below 4000. The patient had a hematocrit level of 31 preoperatively, but during perfusion she had two blood transfusions, giving her an immediate preoperative hematocrit of 39. However, on the 6th postoperative day the hematocrit level dropped to 31 and remained there in spite of two blood transfusions. This was probably due to the Cytoxan. It is too early to evaluate the effects of the perfusion in this patient.

#### *Leg Perfusion*

*Case 4.* This 55-year-old white man had a small black lesion removed from his left foot on

August 20, 1958, at a local hospital. The pathologist reported "malignant melanoma." He was transferred to the University Medical Center, and examination revealed four to five more black nodules in a satellite fashion on the lateral aspect of the left foot. On September 9, 1958, a wide excision of the lesions of the foot with application of a split thickness skin graft was performed, followed by a radical groin dissection and perfusion of the lower extremity with 40 mg. of nitrogen mustard, using the femoral artery and vein. Postoperatively minimal sloughing of the skin flaps in the inguinal area developed but this responded to therapy. He was discharged on the 11th postoperative day. The pathologic study revealed recurrent malignant melanoma in the skin of the left foot with metastasis in three of 28 lymph nodes. Two nodes removed from the bifurcation of the iliac arteries, which was the highest point of node dissection, contained metastatic melanoma.

*Laboratory data.* There was no effect on the white blood cell count, but the platelet count decreased from normal to 186,000 on the 6th postoperative day.

*Follow-up.* The patient was last seen on March 23, 1960, 19 months postoperatively, and he had no evidence of local or distant recurrence. A chest x-ray was negative for evidence of metastases.

#### DISCUSSION

The technique of isolation-perfusion of certain tumors has merit and is being used extensively in various medical centers.<sup>3,8</sup> Judging from our experiences and from the reports of others, the most favorable groups of tumors to treat are the malignant melanomas and the sarcomas located in an extremity. Much success has also been achieved in treating the pain associated with head and neck tumors and in treating recurrent and inoperable tumors of the pelvis.<sup>1</sup> At the present time the alkylating agents consistently give a better response than the other chemotherapeutic agents.

There is ample histologic proof that a certain amount of necrosis of the tumor follows perfusion. This has been obtained by taking biopsy specimens from a tumor days and weeks after perfusion. In each instance the pathologist stated that there was necrosis which was out of proportion to the usual amount seen. In one case the tumor cells had been partially destroyed, leaving only empty spaces in the syncytium of the tissue where the cells had been. This, of course, is very encouraging, but it is not yet

known whether or not total and permanent destruction of tumors by perfusion can be achieved.

By using the technique of isolation-perfusion, it is possible to administer a high concentration of drug with relatively mild systemic side effects in many instances. Many refinements in technique have already been developed. These and others, in conjunction with ever more effective cancerocidal agents, may be expected to achieve a prominent role in the over-all management of neoplasia.

#### SUMMARY

Tumors which are inoperable and which are not amenable to radiation therapy are now being treated by perfusion of an isolated portion of the body with antitumor agents. We have described our own methods of perfusion, discussed the drugs used and their side effects and have presented illustrative cases. In our experience, the alkylating agents are the most effective drugs, and the melanomas and the sarcomas are the most susceptible tumors.

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## ISLET CELL ADENOMAS AND HYPERINSULINISM: A CASE REPORT\*

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The relationship of the pancreas to diabetes was first suspected by Cawley<sup>4</sup> (1788). Langerhans<sup>10</sup> (1869) first described the islet cells of the pancreas. The discovery of insulin by Banting and Best<sup>1</sup> (1922) brought the eventual association between the islet cells and insulin closer. Harris<sup>7</sup> in 1924, noting the similarity of a spontaneous symptom complex to induced hyperinsulinism, postulated that overactivity of the islet tissue would lead to hyperinsulinism.

In 1927, Wilder and associates reported the first case of hyperinsulinism associated with islet cell adenoma. Graham (1929) reported the first successful surgical procedure carried out with resulting cure.<sup>9</sup>

Since that time, Whipple<sup>12</sup> (1944) reported 149 islet cell tumors that had been observed associated with hyperinsulinism, and Howard, Moss and Rhoads<sup>8</sup> (1950) collected material on 224 such tumors that had been surgically removed, and an additional 174 that had been autopsied.

**Pathology.** The first pathologic description of an islet cell tumor was reported by Nichols in 1902, but the clinical manifestations were not observed. Campbell, Graham and Robinson<sup>2</sup> estimated that the incidence of islet cell adenomas was one in 800 or 1000 autopsies, and that 20 per cent were clinically active. The tumors are about equally divided between the sexes. Occurring at any age, they appear to be more frequent in the age group from 40 to 50; however, approximately 90 per cent of those in patients under 30 years of age are associated with hyperinsulinism, whereas those over 60 years of age are rarely hyperfunctioning. They may vary in size from 1 mm. to 15 cm., most varying between 1 and 2 cm. in diameter.

Generally speaking, in most reported series the islet cell tumors are about equally distributed among the head, body and tail of the pancreas. Multiple tumors are noted in approximately

10 per cent of cases; ectopic adenomas in 2 to 5 per cent. Of the cases reported by Howard, Moss and Rhoads<sup>8</sup>, 78 per cent were benign, 12 per cent suspiciously malignant, and 9.3 per cent obviously malignant.

Grossly, islet cell tumors are round discrete tumors, usually but not always encapsulated. On the surface of the gland they appear more deeply colored than the surrounding pancreatic tissue, and a homogeneous grayish pink in color. Microscopically they appear as massive islets of Langerhans with increased vascularity but relatively normal cellular formation. No significant gross or microscopic variations aid in differentiation between functioning and nonfunctioning tumors.

Islet cell carcinomas are distinguishable from the benign adenomas with difficulty by microscopic examination. The presence of metastatic lesions which are apt to be more cellular than the primary lesion is, of course, diagnostic. However, usually a careful search of the primary lesion will show some mitotic activity as well as cellular variation in size.

**Symptomatology.** The symptoms of hyperinsulinism associated with islet cell tumors depend on the excessive secretion of insulin, resulting hypoglycemia, and the decrease below the critical functioning level in the supply of glucose to the brain. The latter results apparently in depression of the oxidative processes in the cells of the central nervous system. Unrecognized and untreated episodes of hypoglycemia may result in extensive and irreversible brain damage.

The symptoms include psychic phenomenon such as anxiety, restlessness, agitation, confusion and coma; neurologic manifestations such as convulsions, tonus, clonus and opisthotonos; and autonomic disturbances such as nausea, sweating, hot and cold flashes and fainting.

The attack is usually preceded by a period of fasting, beginning with a sense of hunger followed by apprehension and secondarily by agitation, profuse perspiration, pallor, dizziness and weakness. The more severe attacks progress to con-

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vulsions and coma. The attacks most frequently occur before breakfast or after excessive exercise in the afternoon, following a long period of inadequate food intake. The patient soon learns that frequent meals and the ingestion of sweets between meals will relieve the symptoms.

**Diagnosis.** The diagnosis is frequently difficult. The pattern is so variable that the patient may be treated for psychiatric illness for long periods of time before hypoglycemia is discovered. Whipple<sup>12</sup> has set forth a triad of symptoms which must be satisfied before diagnosis is exact. These are (1) the symptoms must come on during periods of fasting or after extreme exertion; (2) the blood sugar value during an attack or after 12 hours of fasting must be below 50 mg. per 100 ml.; (3) the symptoms must be relieved promptly by oral or intravenous administration of sugar.

In addition, abnormal glucose tolerance and abnormal epinephrine tolerance may be helpful in establishing the diagnosis. Organic disease outside the pancreas such as hepatic disease and self-administration of insulin must be ruled out. Functional hypoglycemia must be ruled out. This term refers to the nervous regulation of the concentration of blood sugar manifested by hypoglycemia occurring 2 to 4 hours after the

intake of meals of average or high carbohydrate value in patients with associated emotional problems. Early morning or prebreakfast attacks do not occur with functional hypoglycemia. Weakness, hunger, trembling, sweating and rapid pulse usually comprise the symptoms, and they are usually transitory, lasting only 20 or 30 minutes. Coma and convulsions rarely occur.

#### MANAGEMENT

Once the diagnosis is made, the treatment is surgical. The approach is best made through an elongated transverse incision in the upper abdomen about halfway between the xyphoid and the umbilicus (fig. 1A). After exploration of the abdomen, careful attention is given to the pancreas, liver, and regions where ectopic or metastatic tumor may be suspected. Because of the accessibility of the body and tail of the pancreas, this portion is explored first anteriorly, superiorly and inferiorly. If no tumor is located, the head is explored anteriorly. The body and tail are then isolated along with the spleen, and the posterior aspect of the body and tail are explored after it has been brought out of its bed and partially exteriorized. The head of the pancreas and duodenum are then freed up and rotated medially so that the pancreas is held only by the

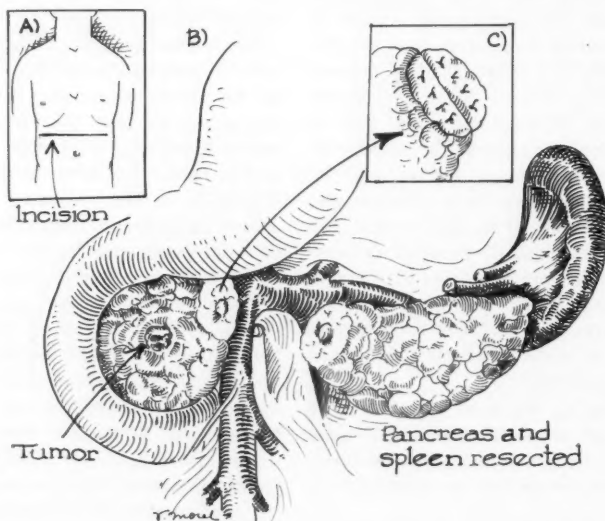


FIG. 1. A. The transverse incision slightly below the midpoint between the umbilicus and the xyphoid. B. The location of the adenoma in the head of the pancreas and the extent of the resection of the distal pancreas and spleen. C. The mattress closure of the neck of the pancreas.



mesenteric vessels. With this exposure, the entire pancreas can be well explored. If a tumor is located in the body, head or tail, it usually can be locally excised. If, however, the tumor is present in the body or tail and it is difficult to excise locally, the body and tail may be resected along with the spleen. In cases in which no tumor can be located, resection of the body, tail and spleen may exhibit the presence of a tumor on pathologic section; or, in rare cases, hyperplasia of the islets may be found in the resected portion with good results. Rather than to resect the entire pancreas when no tumor is located in the resected body and tail, it is believed preferable to defer total pancreatectomy until a later date; for it may develop that the symptoms have been alleviated by distal pancreatectomy.

The wound should be carefully closed with drainage. Regardless of whether a wedge resection or distal pancreatectomy has been accomplished, the area should be well drained. Sump drains and rubber tissue drains extending to the region of the resection, to the area posterior to the head of the pancreas, and to the region of the spleen should be utilized.

Preoperative management requires (1) a high protein diet, (2) maintenance of normal serum potassium and phosphate and (3) the improvement of glycogen reserves immediately before surgery. Glucose should be administered before and during the procedure. Fractional blood tests for sugars should be taken during the operative period.

Postoperatively the patients from whom a functioning adenoma has been removed will have a transient hyperglycemia for a period of from 1 to 14 days. Permanent diabetes rarely occurs. Pancreatic fistulae frequently occur but close within a short period of time. During the period of external drainage of pancreatic fluid, the wound is best protected by constant suction.

#### CASE REPORT

J. W. L., Jr. (48289-U. H.), a 32-year-old white male was admitted on May 17, 1959. The history indicated that he had symptoms of hypoglycemia for 2½ years. The first major episode was noted two months prior to admission; he became listless at 7 a.m. that day before breakfast. His wife stated that he just stared at people but did not seem to see them. He later became unconscious and remained so until late in the evening. A glucose drip was given, relieving the unconsciousness.

The following day a glucose tolerance test was performed and again he became comatose. This was later repeated and the blood sugar was as low as 30 mg. per 100 ml. He had no other incidents associated with coma before admission but had a convulsion while driving home from bird hunting in the late afternoon after having failed to eat a noon meal.

The patient stated that he became weak in the afternoon and that his ability to concentrate was diminishing. The systemic review was pertinent only in that he had "patches" before the eyes; he could not recognize people or objects when his blood sugar level was low.

The past history was negative except for a minor injury to the left leg in childhood. The family history revealed no one with similar complaints. The patient smoked two packages of cigarettes daily and drank about five cups of coffee with sugar. Physical examination revealed no significant findings. He had gained about 17 pounds in 2½ years. On May 19, 1959, a fasting blood sugar test done in connection with a glucose tolerance test gave 47 mg. per 100 ml. The curve rose rapidly to 167, but it did not drop as rapidly as one would expect with a functioning adenoma. During the period of hypoglycemia the patient stared fixedly and was slow to answer questions. This state lasted only about 30 minutes, however. About 2 hours later he fell out of bed and became disoriented but did not have convulsions; he did not later remember blood being drawn for a sugar determination. Administration of sweetened orange juice alleviated this episode promptly. He was fasted for 12 hours on May 22; the blood sugar was 38 mg. per 100 ml. He became comatose, had convulsions, rapid pulse, sweating and during the course of the coma, beat his wife. Administration of 20 ml. of 50 per cent dextrose in water relieved the symptoms within 30 minutes. He had no recollection of the attack.

Electrocardiogram, and phosphate and potassium levels were within normal ranges. Adenocorticotrophic hormone treatment was started, 80 units daily for 4 days before surgery.

*Operation.* On May 26, 1959, the patient was taken to surgery. Through an elongated transverse upper abdominal incision, the abdomen was explored. There was no evidence of metastatic disease. The tail and body of the pancreas were explored anteriorly at first and then the anterior portion of the head. Frozen section examination of a nodule in the tail disclosed only an area of fibrosis. The stomach and duodenum were searched for ectopic pancreas; a search was also made for a Meckel's diverticulum containing aberrant pancreas. The tail and body were then explored

posteriorly after freeing the pancreas along with the spleen. This procedure was unrewarding. The head of the pancreas and duodenum were Kocherized and freed back to the mesenteric vessels, exposing the posterior surface of the head of the pancreas. Finally a mass about  $1\frac{1}{2}$  by 1 cm. was palpated between the fingers in the head of the pancreas nearer the anterior surface. It was approached anteriorly and locally excised (fig. 1B). It presented as a homogeneous pale grayish pink mass not entirely encapsulated. The defect was closed, and the body and tail of the pancreas were resected to the left of the superior mesenteric artery along with the spleen (fig. 1B). The defects in the pancreas were sutured with 2-0 black silk, matted, and a sump drain was placed down to the area of the resected distal pancreas (fig. 1B and C). Rubber tissue drains were inserted in the region of the pancreatic head and the splenic bed. The abdomen was closed in layers. Intravenous glucose was given throughout surgery. The blood sugar levels taken during surgery were 193 to 224 mg. per 100 ml. after removal of the tumor and afterwards in the recovery room rose to 345 and 360 mg. per 100 ml. The postoperative course was uneventful except for a pancreatic fistula that persisted for 6 months. The blood sugar remained elevated for 6 days and then approached normal.

When last seen 1 year after surgery, the patient was entirely well, asymptomatic, and the blood sugar fasting was 97 mg. per 100 ml. For a period of time he took narcotics, but does so no longer.

#### SUMMARY

A review of hypoglycemia associated with islet cell adenoma of the pancreas is presented. The difficulty of diagnosis and the importance of fulfilling Whipple's triad are stressed. A case of functioning islet cell adenoma is presented.

In view of the patient's occupation as a pharmacist, the possibility of self-administration of insulin was investigated thoroughly. The operative measures which may be found useful during surgical exploration are stressed.

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## OPERATIVE MANAGEMENT OF FEMORO-POPLITEAL ATHEROSCLEROTIC OCCLUSIVE DISEASE WITH ILLUSTRATIVE CASES\*

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The multiplicity of procedures and prostheses that have been advocated for the treatment of arterial occlusive disease demonstrates that none is completely satisfactory. The purpose of this report is to present a current survey of the various surgical procedures for the treatment of atherosclerotic vascular disease and to evaluate their effectiveness in the critical femoro-popliteal area.

It is generally accepted that almost anything done to the vessels above the external iliacs will be immediately successful, because these relatively inflexible arteries with their large lumens can be thromboendarterectomized or grafted with almost any textile that will act as a blood conduit without early thrombosis. However, the problem becomes much more difficult when the vessel lumen is less than 8 mm. in diameter, such as those below the inguinal ligament. Here the arterial substitute must be long and narrow, and flexible enough to bend over flexion creases without constriction and obstruction of blood flow. In this area, the incidence of immediate thrombosis is highest, and late results most discouraging. Nevertheless, the femoro-popliteal region is the most common location of atherosclerotic disease which is amenable to surgical treatment. Here all the subtleties of diagnostic and surgical technique must be utilized in order to secure a satisfactory result. Good preoperative arteriograms to visualize the extent of the disease process and, most important, to evaluate the adequacy of the outflow tract, are indispensable. If bypass grafts are used, a carefully executed end-to-side anastomosis to prevent constriction is necessary to maintain long term patency. Also, arteries incised for thromboendarterectomy must be closed without constriction of their lumens; otherwise, early thrombosis is inevitable.

Humphries<sup>1</sup> has suggested the administration of vasopressor agents for 48 hours postoperatively

in order to maintain palpable pulses distal to the graft.

In spite of all these refinements, the over-all result of treatment of atherosclerotic disease in the femoro-popliteal area is still far from ideal (table 1).

### VENOUS AUTOGRAFTS

Historically, autogenous vein grafts were used as early as 1898; however, this procedure was discarded because of the prohibitive early thrombosis rate with the end-to-end technique. After the pioneer work of Kunlin,<sup>12</sup> the end-to-side technique was adopted for placing these grafts, with reasonably good immediate patency. It is now considered the procedure of choice by such authorities as Linton, Lord, Grimson and Dale. According to the proponents of this procedure, vein grafting requires meticulous technique, necessitating specific laboratory training and experience for successful implantation. The most recent comprehensive report is that of Dale, DeWeese and Scott.<sup>5</sup> They report 31 autogenous saphenous vein grafts followed for 13 months. Nine thrombosed within 17 days after surgery (29 per cent and four others within 11 months, leaving 58 per cent patent in just over a year. This generally agrees with the results of Lord<sup>15</sup> and others, which show an early high rate of graft thrombosis but fairly acceptable late patency rates, because late occlusion is very rarely due to "graft failure." Dale and coworkers also cite their preliminary experimental work in dogs, in which they implanted autogenous veins, homologous arteries and various synthetic materials (nylon, crimped and noncrimped; Fluffon Dacron; and flanged Dacron and Orlon) as shunt grafts in the femoral area. Early thrombosis rates were: autogenous veins, 40 per cent; homologous arteries 15 per cent; and synthetics 63.8 per cent. "Late" patency rates were: autogenous veins, 57 per cent; homologous arteries, 75 per cent; and synthetics, 19 per cent.

Autogenous saphenous veins are readily avail-

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TABLE 1

*Comparison of early and late patency rates of various surgical procedures used for femoro-popliteal atherosclerotic occlusive disease*

Series	Arterial Homografts		Saphenous Vein Autografts		Synthetic Prosthesis		Thromboendarterectomy	
	Early (1 mo.)	Late	Early (1 mo.)	Late	Early (1 mo.)	Late	Early (1 mo.)	Late
	%	%	%	%	%	%	%	%
Cannon, Barker and Kawakami (1) Group II (Either ant. or post. tibial artery open at operation)							70	(34 mo.) 50
Warren (19)							66	(6 mo.) 55
Dale, DeWeese and Scott (5)	65	(32 mo.) 27	70	(13 mo.) 58				
Crawford, DeBakey, Morris and Garrett (4)	85	(30 mo.) 60			Nylon 86	(24 mo.)	69	(24 mo.) 54
					Dacron 91	Nylon 64 Dacron 75		
Whitman, Janes, Ivins and Johnson (20)	76	(32 mo.) 40			Nylon 74	(19 mo.)		
					Teflon 91	Nylon 26 Teflon 70		
Edwards (7)					Nylon 90	(24 mo.)		
					Teflon 90	Nylon 50 Teflon 50		
Lord and Stone (15)			62	(12 mo.) 50				
Conn and Fain	88	(48 mo.) 61			Teflon 92	(14 mo.)		
					Nylon 86	Teflon 66 Nylon 52		

able and are usually suitable for implantation. If removed carefully, adequate length may be obtained for bypass from the external iliacs to the posterior tibial arteries. Aneurysmal dilatation occurs very rarely in femoral venous shunt grafts, and other degenerative changes should be minimal, because this is autogenous tissue. If early patency rates can be improved, autogenous venous shunts theoretically should approach the ideal procedure for the femoro-popliteal area, with late patency depending only on the progress of the underlying atherosclerotic disease.

#### ARTERIAL HOMOGRAFTS

The era of practical arterial grafting using homografts began in 1949 with Gross's<sup>9</sup> work on coarctation of the aorta. In the ensuing 11 years arterial homografts reached a zenith of popularity and have now been almost discarded, ostensibly because of late degenerative changes.

In spite of their present unpopularity, they remain the standard to which all other procedures are compared. One of their greatest disadvantages has been their lack of ready availability. They are too difficult to obtain, process and store to be universally practical. They are technically very easy to handle and implant by the end-to-side technique. Early patency is good, being 85 per cent in our series.<sup>3</sup> However, late patency leaves something to be desired, ranging from 40 to 60 per cent in reported series up to 4 years. Dale and associates<sup>5</sup> report the poorest results with homografts found in the literature, with an initial patency of 65 per cent, and only 27 per cent patent in 32 months. Szilagyi,<sup>18</sup> Sauvage<sup>17</sup> and others have reported late degenerative changes in homografts consisting of elastic fiber fragmentation with dilatation and aneurysmal formation. Humphries and associates<sup>11</sup> reporting on the results of 525 homografts followed over a 4½-year period, feel that

degenerative changes are a minor cause of late complications and that progress of atherosclerosis is the primary reason for late failure.

#### CASE REPORT

*Case 1.* O. E. Y., a 63-year-old white man, was admitted on August 2, 1956, complaining of progressively increasing intermittent claudication involving both lower extremities for 2 years. Initially this sensation was one of weakness in the calves, but later cramping pain developed which was severe enough to make him stop walking. There was an associated sensation of burning on the plantar surfaces of the feet. Recently he had noticed weakness in the thighs and, fearing that the condition was extending upward, he came to the hospital. The preceding winter he had become aware that his feet became unusually cold, and he had also begun having nocturnal cramps which would waken him from sleep. His general condition had remained good, but he had to discontinue farm work because of bilateral leg pain.

Examination revealed a slightly obese, elderly white man with a somewhat rolling gait which he stated was due to the fact that his calves hurt when they were stretched. The ocular fundi revealed mild tortuosity with irregularity and increased light reflex of the arterioles. There was absence of popliteal, dorsalis pedis and posterior tibial pulsations bilaterally. Femoral pulsations were present and of good quality. Both lower extremities became pale on elevation, with rubor and then cyanosis with dependency over a period of about 3 minutes. Both feet were cool, but of approximately the same temperature. X-rays of the legs revealed calcification along the course of the posterior tibial vessels. Femoral arteriograms revealed segmental occlusion of the superficial femoral artery from its bifurcation to the adductor hiatus, bilaterally (fig. 1A).

On September 10, 1956, exploration revealed complete obliteration of the left superficial femoral artery. An arterial homograft was used to shunt this obliterated area, implanting the proximal end to the side of the common femoral artery and the distal end to the side of the popliteal artery (fig. 1B). The length of this arterial homograft was 35 cm. There was free flow of blood through the graft at the time of anastomosis, with immediate bounding posterior tibial and dorsalis pedis pulsations. An operative arteriogram demonstrated free flow of opaque media through the shunt with good visualization of the peripheral vessels. It was recognized at that time that the popliteal anastomosis was not placed distally enough to bridge large atherosclerotic plaques in the popliteal artery (fig. 1C).

Approximately 1 year later this patient was re-admitted complaining of gradual recurrence of symptoms in the left leg over a 3-month period. Re-exploration revealed complete occlusion of the distal popliteal artery due to progression of atherosclerotic disease. Further grafting was not feasible; consequently, left lumbar sympathectomy was done with partial relief of symptoms.

Most occlusions occur during the first year. There has been some experimental evidence to show that operative manipulation may hasten the progress of atherosclerosis.

Homografts will probably be used much less frequently in the future because of the fear of late degenerative changes leading to aneurysmal formation with secondary rupture or occlusion.

#### SYNTHETIC PROSTHESES

Contemporary interest in plastic arterial prostheses began almost concurrently with the application of successful arterial homografts. Because of the difficulty in obtaining and processing suitable homografts it was realized that synthetic materials must be fabricated to make arterial grafting procedures universally applicable. During the past 10 years, many plastic vascular substitutes have been introduced by their enthusiastic, vociferous proponents, including Vinyon N, Orlon, Ivalon, nylon, Dacron and Teflon. These materials have been further identified as braided, woven, knitted, calendered, crimped, elasticized, molded, tubed and seamed. Practically all combinations have now been discarded for use in the femoro-popliteal region with the exception of crimped woven Teflon and flexible knitted Dacron tubes. Both of these synthetics can be implanted with an extremely low incidence of initial thrombosis and up to 2-year patency rates reminiscent of early optimistic homograft reports before degenerative changes were noted. Degenerative changes have been demonstrated in all of the leading synthetics.<sup>8</sup> Atheromatous formation in the neo-intima of Dacron has been reported after 1 year, and ulceration and sloughing of the neo-intima has been noted in Teflon grafts. Knitted grafts have the disadvantage of high porosity, allowing appreciable blood loss when clamps are removed, in spite of preclotting. The relatively large interstices, however, allow ingrowth of fibrous tissue to anchor the neo-intima securely. Woven grafts, because of low porosity, "sweat" only



slightly when clamps are removed, but because of small interstices the neo-intima is not anchored securely and may slough, causing distal obstruction and graft thrombosis. Teflon has the least

tissue reactivity of any of the synthetics, resulting in a thinner neo-intima, which is extremely important in replacing vessels of 8 mm. or less in diameter.<sup>10</sup>

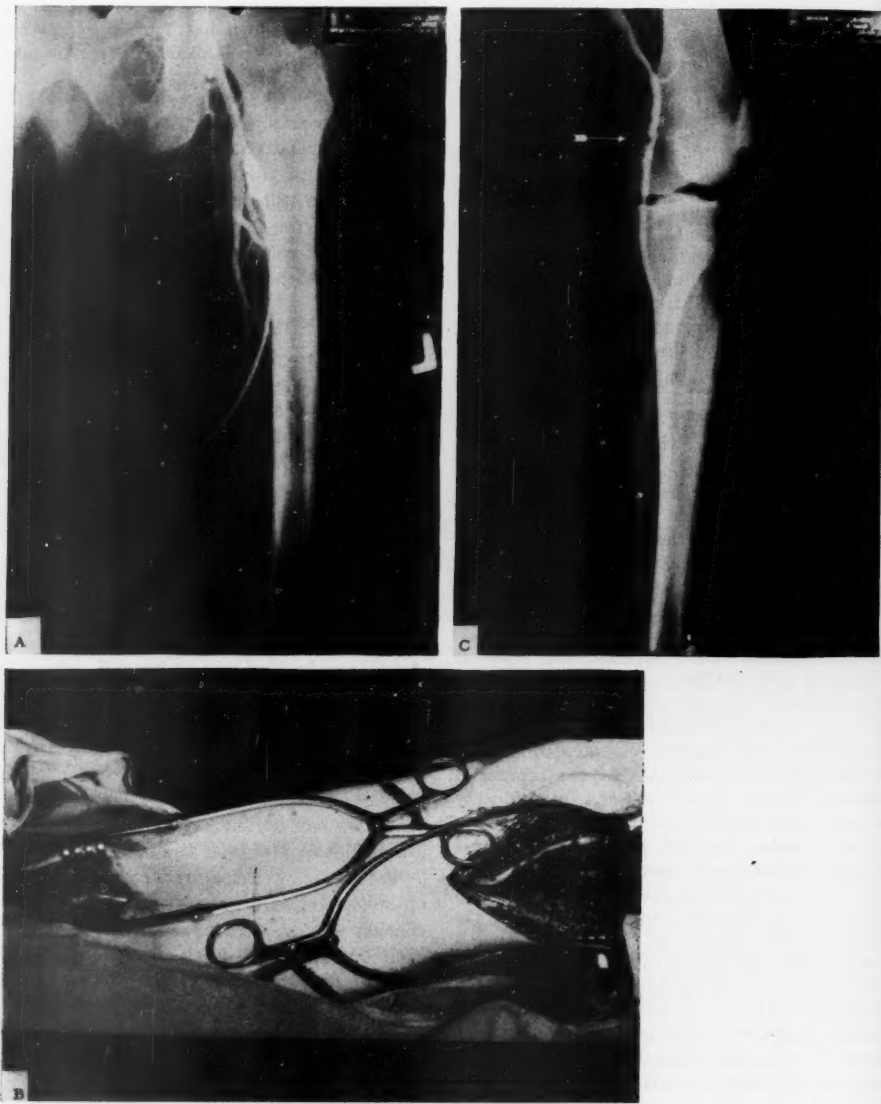


FIG. 1. Case 1: A. Preoperative left femoral arteriogram showing obliteration of the superficial femoral artery from its origin to the adductor hiatus. B. Femoral arterial homograft in place. End-to-side anastomoses accomplished to the common femoral and popliteal arteries. The popliteal anastomosis is to the right. C. Operative arteriogram demonstrating extensive atherosclerotic involvement of the popliteal artery distal to the anastomosis.

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## CASE REPORT

Case 2. W. J. W., a 49-year-old white man, was admitted complaining of gradually increasing intermittent claudication over a 3-year period. At the time of admission he could walk only 1 block without severe bilateral calf pain, necessitating rest for relief.

On physical examination both lower extremities were cool, with moderate trophic changes. Popliteal and pedal pulses were absent bilaterally.

Femoral pulsations were palpable and of good quality. Bilateral femoral arteriograms revealed complete obstruction of the superficial femoral artery from the common femoral bifurcation to the popliteal. On July 7, 1959, an arterial homograft was placed end-to-side from the left common femoral to the left popliteal artery. There was immediate restoration of distal pulses. On August 31, 1959, a  $\frac{5}{16}$ -inch crimped woven Teflon (Edwards) graft was implanted end-to-side from the

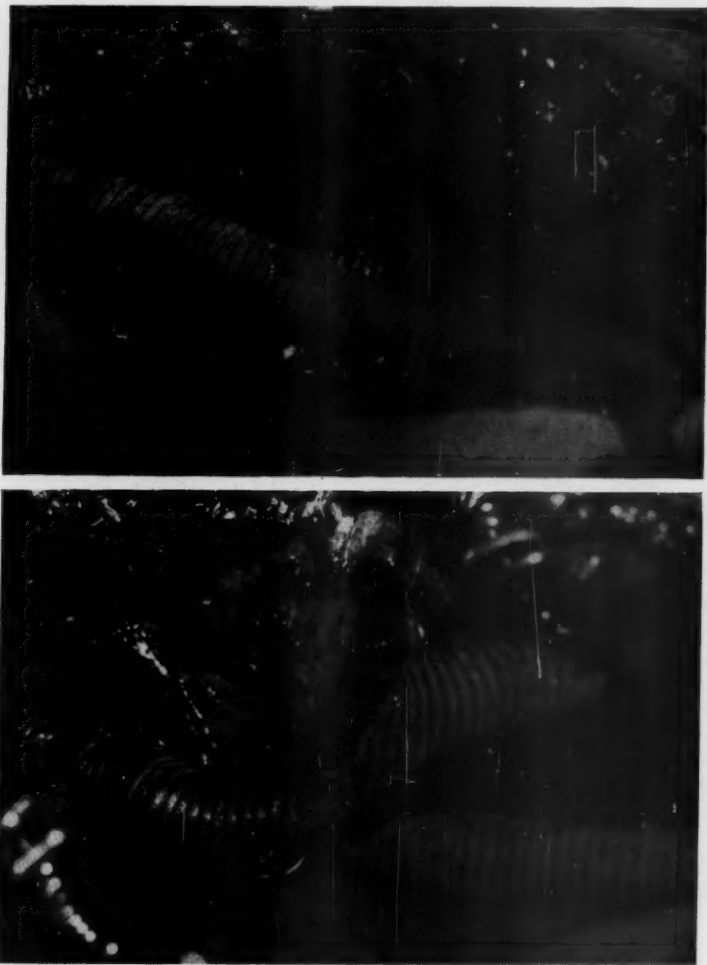


FIG. 2. Case 2: *Top*. Proximal end-to-side anastomosis of Teflon graft to common femoral artery thrombosed 3 months postoperatively. Fibrous tissue sheath can be seen immediately above graft. Connective tissue had not penetrated interstices of graft wall. *Bottom*. Teflon graft has been dissected from the artery at the common femoral anastomosis, showing thrombus completely filling its lumen. The neo-intima had become detached from the graft and was adherent to the thrombus.

right common femoral artery to the right popliteal artery. Distal pulses were immediately palpable. After this last operation the patient was able to walk long distances without claudication and, despite our admonitions, resumed his occupation as a butcher, standing on his feet for 8 to 10 hours daily.

On December 7, 1959, he returned to the hospital complaining of gradually increasing pain in the right calf and coolness of the right foot of 3 weeks' duration. Examination revealed that popliteal and pedal pulses were absent on the right, but were present and of good quality on the left. The right foot was cool, with bluish discoloration of the right first toe. Right femoral arteriogram demonstrated complete occlusion of the graft. Consequently, on December 23, 1959, the Teflon graft was exposed and found to be completely thrombosed with thrombosis extending proximally into the right iliac artery and distally into the popliteal. The graft was lying in a smooth fibrous tunnel which had the shape of its accoridian pleats, but absolutely no adherence to the graft itself (fig. 2, *top*). Fibrous tissue had not penetrated the interstices of the graft wall. On opening the graft longitudinally, the neo-intima was found to be adherent to the thrombus but was not attached to the graft wall, permitting it to slide in and out without difficulty (fig. 2, *bottom*). It is postulated that the neo-intima may have become detached from the graft wall, slid distally and obstructed the popliteal artery, thereby causing proximal thrombosis of the graft. The Teflon prosthesis was removed and a homograft placed in the same location. This remained patent until the patient died of a coronary occlusion on August 6, 1960.

According to Newton, Stokes and Butcher,<sup>16</sup> all grafts with the exception of those of autogenous tissue lose their elasticity and flexibility within 6 months after implantation. This is believed by Edwards<sup>7</sup> to be a major cause of late graft failure, and he is now advocating endarterectomy as the procedure of choice in the femoro-popliteal region, particularly if arterial occlusion occurs across flexion areas.

#### THROMBOENDARTERECTOMY

Thromboendarterectomy was popularized in Europe by dos Santos<sup>6</sup> and Leriche<sup>14</sup> in 1948. Cannon and Barker<sup>2</sup> and Wylie<sup>21</sup> have been the chief proponents of the procedure in this country.

The dos Santos single arteriotomy type of endarterectomy has been largely replaced by the semi-closed method. Using this technique, Cannon, Barker and Kawakami<sup>1</sup> report good to fair

results in 66 per cent of 45 cases followed for 1 to 5 years. Cannon advocates concomitant lumbar sympathectomy, which casts some suspicion on the merits of thromboendarterectomy as a definitive procedure, if it requires a supplementary operation. The multiple arteriotomy, semi-closed technique, is rather meticulous, as the plane of cleavage may include intima and media depending on the extent of the atherosclerotic process. The intima distal to the endarterectomy must be carefully sutured to the vessel wall to prevent dissection. Postoperative anticoagulant therapy is necessary to prevent early thrombosis in the denuded segment.

Endarterectomy is appealing because it has the advantage of opening a channel in the patient's own artery and restoring blood flow without implanting foreign material. Also, these vessels usually retain enough elasticity to bend in flexion areas without kinking or buckling, and the long term patency rate is relatively good. The disadvantages are a high early thrombosis rate in spite of anticoagulants and also the attendant complications of anticoagulant therapy. Primary closure of the arteriotomy incision decreases the vessel lumen appreciably, thereby impeding blood flow through this traumatized, constricted segment. Recently the insertion of an autogenous vein patch graft between the two sides of the incision in the artery has been advocated. This necessitates two parallel suture lines to close the arteriotomy, but increases the intraluminal diameter to any size desired, depending on the width of the interposed vein segment. This technique also allows longer arteriotomies with direct removal of atherosclerotic material, resulting in smoother endarterectomized segments than can be obtained with blind stripping. In some cases of obstruction, in which medial thickening is producing stenosis of the artery with only minimal intimal involvement, endarterectomy may not be necessary; simply removing the organized thrombus and increasing the intraluminal diameter with an autogenous vein patch may successfully restore blood flow without denuding the vessel wall.

#### CASE REPORT

Case 3. J. L. B., a 50-year-old Negro man, was admitted complaining of gradually increasing intermittent claudication of 1 year's duration. For the previous month he had noted severe left

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A. BEFORE



B. AFTER



FIG. 3. Case 3: A. Preoperative left femoral arteriogram with illustration demonstrating obstruction of proximal popliteal artery. B. Postoperative left femoral arteriogram with illustration demonstrating increased intraluminal diameter of popliteal arterial segment at site of previous constriction.

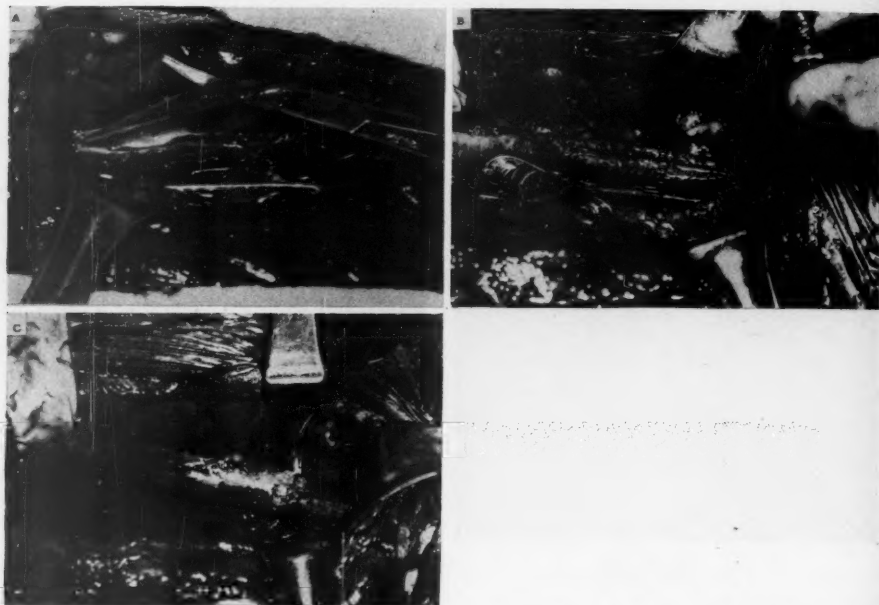


FIG. 4. *A.* Arteriotomy of constricted popliteal artery (Case 3). Autogenous vein patch graft has been sutured proximally and distally and is being held by the hemostat out of the incision in the artery. *B.* Autogenous vein graft has been sutured to the sides of the popliteal artery, closing the arteriotomy. *C.* Arterial clamps have been removed and blood flow restored. Intraluminal diameter is approximately  $1\frac{1}{2}$  times normal size.

calf pain after walking only 2 blocks. Physical examination revealed the left leg and foot to be cooler than the right, with mild trophic changes. There was absence of popliteal and pedal pulses on the left, with good femoral pulsation. All peripheral pulses were present and of good quality on the right. A left femoral arteriogram demonstrated occlusion of the proximal popliteal artery (fig. 3A). The distal popliteal, posterior and anterior tibial arteries were well filled with contrast media.

On August 21, 1960, surgical exploration revealed the left popliteal artery to be firm, thrombotic and pulseless from the level of the adductor hiatus to midpopliteal. On opening this vessel it was found to contain an organized thrombus. At the distal end of this thrombus there was a constriction of the popliteal artery, caused principally by segmental thickening of the media, with only minimal atheromatous involvement of the intima. The arteriotomy was extended through this area and all thrombotic material removed. A 10-cm. segment of left saphenous vein was removed and opened its entire length longitudinally. This opened vein segment was then inserted into the popliteal artery as a patch graft (fig. 4A). Because this was a relatively narrow

saphenous vein, its entire opened width was utilized, suturing the sides of the graft to the respective sides of the host artery, using 4-0 arterial silk (fig. 4B). This actually increased the intraluminal diameter of the artery so that it was greater than that of the vessel proximally and distally (fig. 4C). On removal of the clamps, blood flow was excellent through this segment, with bounding distal pulses. Anticoagulants were not used postoperatively, since the intima had not been denuded. Postoperative arteriogram demonstrated a significant increase in the intraluminal diameter of the previously occluded arterial segment (fig. 3B).

Flexible, elastic autogenous tissue was used to increase the intraluminal diameter of this constricted popliteal artery to greater than normal size. It is anticipated that long term patency will be good, in spite of the fact that it lies over a flexion area.

#### EXPERIMENTAL

In our laboratory one of us (W. R. F.) recently investigated the practicality of using the intact



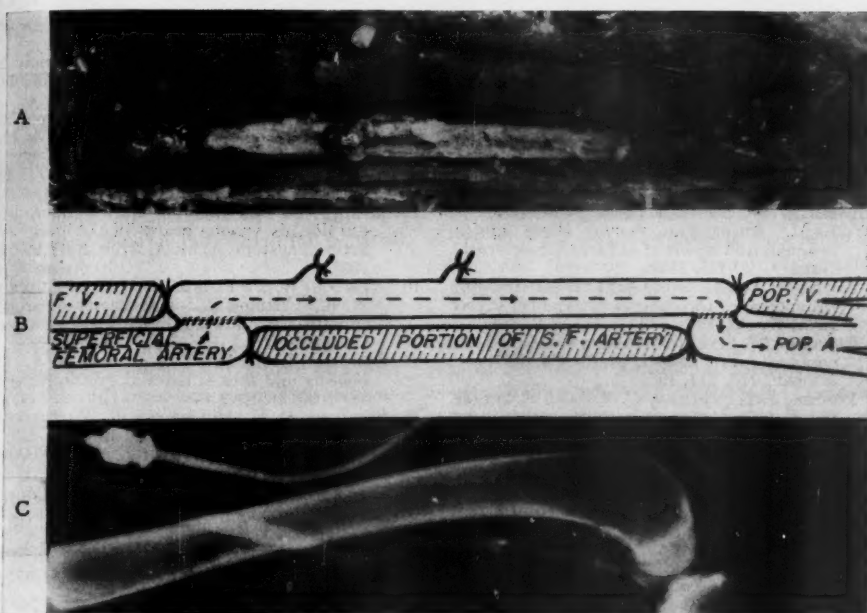


FIG. 5. A. Femoro-popliteal vein is ligated proximally and distally with anastomoses to the adjacent femoral and popliteal arteries. Superficial femoral artery has been occluded by ligatures. B. New route of blood flow shown diagrammatically. C. Femoral arteriogram taken 6 months postoperatively.

femoral vein to bridge femoro-popliteal arterial occlusion. After occluding the superficial femoral artery in dogs, side-to-side anastomoses were performed between the femoral artery and vein proximally and the popliteal artery and vein distally as shown in figure 5, forming a typical bypass. Major venous tributaries were ligated and valves disrupted by inserting an intraluminal stripper. This procedure has the advantage of using autogenous vessels without displacing them or disrupting their blood supply, and may be applied to the even more critical anterior and posterior tibial vessels. Preliminary results are encouraging, and a complete report will be forthcoming in the near future.

#### SUMMARY

At best, all the surgical procedures advocated for femoro-popliteal atherosclerotic occlusive disease are palliative, because only the complications of atherosclerosis are treated, and not the underlying progressive disease. The long range outlook for these patients is poor; however, if an extremity can be saved or made usable for several

years, then palliative procedures are certainly worthwhile. The problem is to devise techniques and materials that will not degenerate more rapidly than the host vessel. All foreign materials implanted to date, including homografts, heterografts and synthetics, have shown degenerative changes, due to either inherent defects in the material or to tissue reactivity, which must eventually result in late "graft failure." Autogenous veins, because of their ready availability, lack of antigenicity and retained viability, should be the best material to use, either as bypass conduits or patch grafts. Thromboendarterectomy combined with an autogenous vein patch graft to increase intraluminal diameter may at the present time be the best procedure to use in the femoro-popliteal region, particularly over flexion areas.

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## GASTRIC ULCER\*

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Jackson, Mississippi

Therapy of gastric ulcer remains a highly controversial problem. The literature is replete with staunchly supported and often diametrically opposed opinions. Thus an appraisal of the problem seems in order.

The usual gastric ulcerations are of two types:

1. Ulceration occurring in an area of infiltration or induration which is pathognomonic of malignancy until histologically proven otherwise and thus demands *immediate surgical intervention*.

2. Ulceration with the typical gross appearance of benign peptic ulcer. Numerous studies have shown the incidence of hidden malignancy in this group of grossly benign gastric ulcerations to be at least 10 per cent, despite the diligent use of diagnostic procedures.<sup>5, 5, 7, 10, 11</sup>

It is this latter group of so-called benign gastric ulcers or "peptic ulcer of the stomach" about which there is the greatest difference of opinion and to which this discussion will be confined.

## SYMPTOMATOLOGY

This disease is prone to occur in men, but certainly there is not the striking sex differential that one finds in duodenal ulcer. Although occurring in all age groups, gastric ulcer is more often found in the sixth decade. The clinical picture is not particularly diagnostic but does form the basis for rational diagnostic procedures. Varying pain, usually epigastric, is present in 90 per cent of the cases; vomiting is present in 50 per cent; hematemesis and melena are found in approximately one-fourth (fig. 1).

The usual radiologic locations are depicted in figure 2. The site of predilection is the lesser curvature where 50 per cent of gastric ulcers occur. Twenty per cent occur in the prepyloric area and another 20 per cent in or about the pyloric channel. It is fortunate that gastric ulceration is no more frequent in the right half of the stomach, for this is a *radiologic blind spot* and disease here can be difficult to detect. Greater curvature

ulcers, though infrequent, should be considered malignant and demand immediate surgery.

The differential diagnosis between a benign gastric ulcer and an *ulcerocancer*, or ulcer which is grossly and clinically benign but histologically malignant, is obviously of the utmost importance but remains a perplexing problem. In general, clinical evaluation, including age, size and location of the ulcer, duration of symptoms and weight loss, are of no differential value. Gastric analysis is of little help; however, histamine achlorhydria strongly points to malignancy and demands immediate surgery.

Although a few extol the virtues of gastroscopy, most agree that it is an ancillary diagnostic facility of limited usefulness. It is indeed difficult to believe that one can look through a long

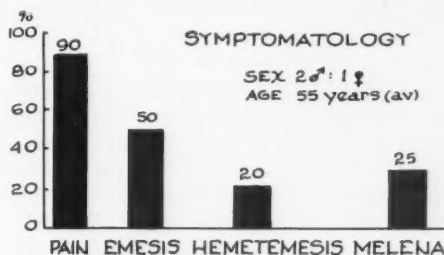


FIG. 1. Symptoms not pathognomonic, but point to rational diagnostic procedures.

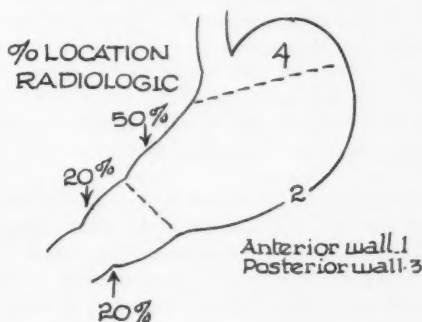


FIG. 2. Usual radiologic locations of gastric ulcer.

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	NUMBER OF CASES	SURGERY	MALIGNANCY	RECURRENCE	MEDICAL CURES
COMFORT-1952	414	34%	10.4%		20%
JORDAN-1953	1000	58%	8.8% (RECURRENT) 16%	33%	
TANNER-1953	498	50%	PERMANENTLY HEALED 25%		
HAYES-1955	231	42%			33%

FIG. 3. Results of medical management. While complete healing is attained in 20 to 30 per cent of cases, 10 per cent with clinically undetectable malignancy are losing their chance for cure!

tube and tell whether an ulcer is benign or malignant with a high degree of accuracy, when surgeons and pathologists with the opened specimen in their hands find that they are frequently unable to do so.

There has been much emphasis recently on gastric cytology. There is general agreement, however, that whereas a positive cytologic diagnosis is of real significance, a negative diagnosis means little or nothing. Fluoroscopy and x-ray examination remain our diagnostic bulwark, but we cannot expect a histologic diagnosis from such an examination.

#### MEDICAL MANAGEMENT

An evaluation of medical treatment in gastric ulcer is indicated in figure 3. Jordan<sup>11</sup> of the Lahey Clinic has reported on 1000 cases. In this group surgery became necessary in 58 per cent of the cases because of intractability, failure to heal, hemorrhage and other causes. Despite the best use of diagnostic procedure, an 8.8 per cent incidence of malignancy in these grossly benign lesions was present! It is interesting that there was a 33 per cent incidence of recurrence in those not treated surgically and that the incidence of malignancy in recurrent ulcers jumped to 16 per cent. Swynnerton and Tanner<sup>13</sup> of England, in analyzing 498 cases, found that surgery became necessary in half but that permanent healing could be attained by medical therapy in only 25 per cent.

Comfort and associates<sup>3</sup> of the Mayo Clinic selected 414 cases which were gastroenterologically considered ideal for medical treatment. In this group which seemed ideal for conservative treatment, surgery became mandatory in 34 per cent. There was an incidence of hidden malignancy of 10.4 per cent, and medical cures were attained in only 20 per cent! Hayes<sup>5</sup> of Yale

#### 5 YEAR SURGICAL CURE

##### MALIGNANT GASTRIC ULCER

Cleveland Clinic.....	46% (11 of 24)
Mayo Clinic.....	60% (33 of 55)
M.G.H.....	50% (5 of 10)

FIG. 4. Surgical cure rate is vastly greater in the malignant gastric ulcer group as compared to frank carcinoma of the stomach.

reports medical cures in only 33 per cent of gastric ulcers. Even Palmer of Chicago who is certainly one of the most staunch supporters of medical therapy in gastric ulceration admits that such therapy is associated with a 40 to 50 per cent incidence of recurrence. Common sense tells us that many of the so-called recurrences are ulcers which have never healed.

These studies and others show that there are decided limitations to medical therapy in gastric ulcer, for one can expect an excellent result with complete and prolonged healing in only 20 to 30 per cent. While this is being attained, 10 per cent of the group will present obvious cancer.

The universally poor results of surgery in full-blown gastric carcinoma have made many physicians quite pessimistic about curing any gastric malignancy. The picture is certainly not as dismal in the malignant gastric ulcer group in which early surgery results in a 50 to 60 per cent 5-year cure<sup>14</sup> (fig. 4).

#### THERAPY

Since rational therapy of gastric ulcer must be based upon (1) the incidence of malignancy and our lack of ability to detect it and (2) the failure of medical treatment, immediate surgery should be advised in 75 to 80 per cent of cases. Certainly, this is in direct contradistinction to the usual therapy of duodenal ulcer in which conservatism

is the keynote and surgery becomes necessary in only 10 or 15 per cent.

In a minority group, a 2- to 4-week period of medical therapy should be instituted. If there has not been dramatic improvement in 2 weeks and complete healing of the ulcerative lesion in 4 weeks, prompt surgery should be advised in this group. Included in the group selected for initial medical therapy with close observation are:

1. The elderly poor risk patient in whom the risk of gastrectomy seems to be as great or greater than the risk of malignancy.

2. Acute or stress ulcers (a) in which the history is of short duration and there has been severe psychic or emotional disturbance; (b) following severe trauma, as burns or neurosurgical procedures; (c) precipitated by prolonged drug therapy, especially corticoids, aspirin and similar drugs.

3. Cases in which there is doubt from the initial radiologic examination as to whether or not there is actual gastric ulceration in the distal half of the stomach. It is to be emphasized that the right half of the stomach is notoriously a radiologic blind spot, making surgical exploration even with inclusive radiologic findings often mandatory in this region when malignancy is suspected.<sup>9</sup>

4. Pyloric channel ulcerations without obstruction are almost uniformly benign and should be treated as duodenal ulcers. They are more difficult to heal with medical therapy, however.

Multiplicity of gastric ulceration or association with an active duodenal ulcer usually but not in-

variably points to benignancy, but surgical therapy is best for such a strong ulcer diathesis.

#### SURGICAL APPROACH

As it is often impossible at the time of operation to differentiate a malignant from a benign gastric ulcer, operation devised to cope with either eventuality is employed.<sup>14</sup> Thus the greater omentum, gastrocolic and gastrohepatic ligaments are included in resection of the lower two-thirds of the stomach in the usual distal ulcer (fig. 5). Intestinal continuity is best re-established by direct gastroduodenostomy (Billroth I procedure), since this procedure affords better post-operative nutrition with fewer and milder dumping sequelae. Occasionally in the obese patient, a Billroth II type of anastomosis will be the one of choice.

Although infrequent, the surgical treatment of the juxta-esophageal ulcer is more difficult. Usually it is possible to excise the ulcerative process and still leave adequate stomach to serve as a reservoir. This can be effected by going high on the lesser curvature and preserving a longer segment on the greater curvature side (fig. 6). Frozen section should be employed, since this obviously would be inadequate for a malignant lesion. Priestley and co-workers,<sup>2</sup> in a thorough study of 50 consecutive juxta-esophageal ulcers (occurring within 4 cm. of the esophageal opening), found only three, or 6 per cent, of the 50 to be malignant. Rarely should proximal gastrectomy be employed because of the danger of reflux

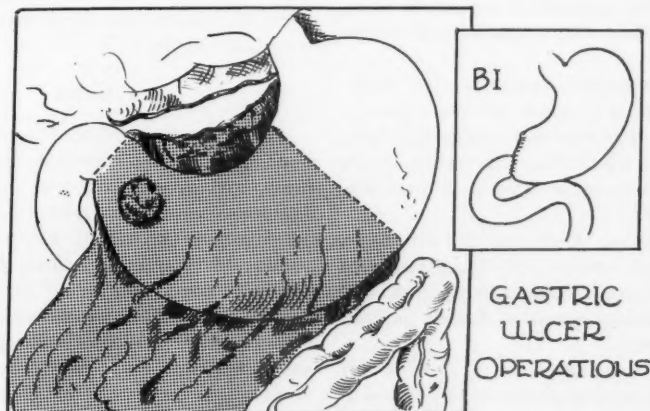


FIG. 5. Removal of omenta and regional lymph nodes is essential, since it may be impossible, even at the time of operation, to differentiate between a malignant and benign gastric ulcer.



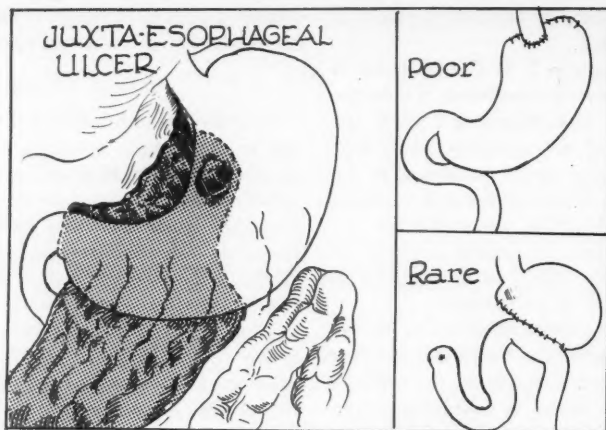


FIG. 6. The vast majority of juxta-esophageal ulcers can be resected and adequate gastric reservoir preserved.

esophagitis which can be so disabling. Very rarely the Madlener operation in which the ulcer is not resected is performed. Multiple biopsies must be taken from the ulcer, and careful follow-up is essential to avoid overlooking malignancy.

#### COMPLICATIONS

Postoperative complications following subtotal gastrectomy for gastric ulcer are fortunately not common and can be handled quite satisfactorily. In approximately 3 to 5 per cent of cases there may be a major complication such as:

1. Leakage from the duodenal stump or at the site of gastroduodenal anastomosis, which is quite unusual following gastrectomy for gastric ulcer, since one is dealing with a sound duodenum in most cases.

2. Mild postoperative pancreatitis as determined by elevation of serum amylase occurs in 3 to 5 per cent of gastrectomies for gastric ulcer; however, severe fulminating pancreatitis occurs rarely, which is fortunate because it often terminates lethally.<sup>6</sup>

3. Malfunctioning stoma usually responds to prolonged gastric suction with maintenance of electrolyte and protein balance, but occasionally requires a secondary operation, usually anterior gastrojejunostomy.

4. Although dumping occurs in 15 to 30 per cent of cases, it is severe and a major problem in only 2 per cent. It is less common and less severe after Billroth I than after Billroth II procedures.

Most often it is transitory in nature and can usually be controlled by avoiding whole milk products and sweets. Better nutrition is afforded by a Billroth I anastomosis; thus severe post-operative weight loss is usually not a problem following gastrectomy for gastric ulcer.

All in all, the results of gastrectomy for gastric ulcer are completely satisfactory in 90 to 95 per cent of patients, and certainly far superior to the results of conventional medical therapy, in which only one in three is completely cured and a recurrence rate of approximately 50 per cent can be expected. Entirely too much emphasis has been placed by the internist on postgastrectomy effects, for the morbidity and adjustment required with gastrectomy are much less than those of medical therapy.

#### SUMMARY

It is obvious that gastric ulcer differs from duodenal ulcer in many respects including age of patients, sex ratio, incidence of malignancy and response to medical therapy. Gastric and duodenal ulcer are two entirely different diseases and should not be blandly grouped together under the term "peptic ulceration." Duodenal ulcer is essentially a medical disease; gastric ulcer is primarily a surgical disease. Although operation is not necessary in every patient as has been advocated by some, certainly it should be strongly considered in every case and deferred only by compelling circumstances.

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